

UNSTABLE PATTERNS IN AUTOCATALYTIC REACTION-DIFFUSION-ODE SYSTEMS

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ABSTRACT. The aim of this paper is to contribute to understanding of the pattern formation phenomenon in reaction-diffusion equations coupled with ordinary differential equations. Such systems of equations arise, for example, from the modeling of interactions between proliferating cells and diffusing growth factors. We focus on stability of solutions to an initial-boundary value problem for a system consisting of a single reaction-diffusion equation coupled with an ordinary differential equation. We show that such systems exhibit diffusion-driven instabilities (Turing instability) under the condition of autocatalysis of non-diffusing component. Nevertheless, there exist no stable Turing patterns, *i.e.* all continuous spatially heterogeneous stationary solutions are unstable. In addition, we formulate instability conditions for discontinuous patterns for a class of nonlinearities.

1. INTRODUCTION

Diffusion-driven instability (DDI), called also *Turing-type instability*, is a phenomenon in mathematical biology, which has been often used to explain *de novo* pattern formation. Let us recall that DDI is a bifurcation that arises in a reaction-diffusion system, when there exists a spatially homogeneous solution, which is asymptotically stable with respect to spatially homogeneous perturbations, but unstable to spatially heterogeneous perturbations. Models with DDI describe then a process of a destabilization of stationary spatially homogeneous steady states and evolution of spatially heterogeneous structures towards spatially heterogeneous steady states. The ideas on DDI have inspired development of a vast number of mathematical models since the seminal paper of Turing [36], providing some explanations on symmetry breaking and *de novo* pattern formation during development, explaining shape of animal coat markings, and predicting oscillating chemical reactions, see *e.g.* [22] and references therein.

In particular, the following system of reaction-diffusion equations

$$u_t = \varepsilon \Delta u + f(u, v), \quad v_t = D \Delta v + g(u, v),$$

considered in a bounded domain and supplemented with boundary and initial conditions, has been proposed as a mathematical model describing the diffusion-driven instability. Here, the unknown function $u = u(x, t)$, sometimes called the *activator*, diffuses with a very small diffusion coefficient $\varepsilon > 0$. On the the hand, $v = v(x, t)$ describes the density of the *inhibitor* and the corresponding equation contains a large constant diffusion coefficient $D > 0$.

In several models, however, the diffusion of u is either so small that it is practically negligible or u does not diffuse at all, which leads to a system of one ordinary differential equation coupled with one reaction-diffusion equation. Such systems of equations arise *e.g.* from modeling of interactions between cellular processes and diffusing growth factors, see [18, 13] for derivation of such mathematical models, [9, 12, 15, 16, 17] for some biological

applications and [14] for their mathematical analysis. Such models are different from classical Turing-type models and the spatial structure of the pattern emerging from the destabilization of the spatially homogeneous steady state cannot be determined based on linear stability analysis. Therefore, the existence and stability of spatially heterogeneous patterns arising in models exhibiting diffusion-driven instability, but consisting of only one reaction-diffusion equation is an interesting issue. As shown in [14] for a particular example of a reaction-diffusion-ODE system, it may happen that there exist no stable Turing-type patterns and the emerging spatially heterogeneous structures have a dynamical character. In numerical simulations, solutions having the form of periodic or irregular spikes have been observed.

The aim of this work is to investigate to which extent these results, obtained in [14], concerning the instability of all stationary structures can be generalized to reaction-diffusion-ODE models with a single diffusion operator.

In the remainder of this paper, we focus on the following two-equation system

$$(1.1) \quad u_t = f(u, v), \quad \text{for } x \in \overline{\Omega}, \quad t > 0,$$

$$(1.2) \quad v_t = \Delta v + g(u, v) \quad \text{for } x \in \Omega, \quad t > 0$$

in a bounded domain $\Omega \subset \mathbb{R}^N$ for $N \geq 1$, with a sufficiently regular boundary $\partial\Omega$, supplemented with the Neumann boundary condition

$$(1.3) \quad \partial_\nu v = 0 \quad \text{for } x \in \partial\Omega, \quad t > 0,$$

where $\partial_\nu = \partial/\partial\nu$ and ν denotes the unit outer normal vector to $\partial\Omega$, and initial data

$$(1.4) \quad u(x, 0) = u_0(x), \quad v(x, 0) = v_0(x).$$

The nonlinearities $f = f(u, v)$ and $g = g(u, v)$ are arbitrary C^2 -functions that satisfy certain natural (biologically motivated) assumptions. Notice also that the diffusion term in equation (1.2) could have the form $D\Delta v$ with a constant diffusion coefficient $D > 0$, however, after rescaling the time variable and the functions f and g , we can assume that $D = 1$.

By a standard theory (see *e.g.* [29] and the beginning of Section 4), the boundary value problem (1.1)-(1.4) has a unique local-in-time solution *e.g.* for every $u_0, v_0 \in L^\infty(\Omega)$. The aim of this work is to investigate the stability properties of stationary solutions.

The paper is organized as follows. In Section 2, main results of this paper are formulated. Section 3 provides examples of reaction-diffusion-ODE systems considered in mathematical biology, which fit the framework of the theory developed in this work. Proofs of the results are presented in Sections 4 and 5. Section 4 is devoted to showing instability of continuous stationary solutions under so-called autocatalysis and compensation conditions. Moreover, for the instability of discontinuous solutions additional conditions on the model nonlinearities are required. In Section 5, constant and non-constant stationary solutions of considered models are characterized and it is shown that they satisfy the conditions formulated in Section 4. Appendix contains additional information on the model of early carcinogenesis which was the main motivation for the research reported in this work.

2. RESULTS AND COMMENTS

2.1. Instability of steady states. The main goal of this paper is to formulate assumptions on stationary solutions of problem (1.1)-(1.4), which lead to their instability. Then,

we show that such assumptions are satisfied in a natural way in reaction-diffusion-ODE systems modeling the Turing instability.

First, we consider *regular stationary solutions* (U, V) of problem (1.1)-(1.3), namely, we assume that there exists a solution (not necessarily unique) of the equation $f(U(x), V(x)) = 0$ that is given by the relation $U(x) = k(V(x))$ for all $x \in \Omega$ with a C^1 -function $k = k(V)$. Thus, every regular stationary solution (U, V) of the boundary value problem

$$(2.1) \quad f(U, V) = 0 \quad \text{for } x \in \overline{\Omega},$$

$$(2.2) \quad \Delta V + g(U, V) = 0 \quad \text{for } x \in \Omega,$$

$$(2.3) \quad \partial_\nu V = 0 \quad \text{for } x \in \partial\Omega$$

satisfies the elliptic problem

$$(2.4) \quad \Delta V + h(V) = 0 \quad \text{for } x \in \Omega,$$

$$(2.5) \quad \partial_\nu V = 0 \quad \text{for } x \in \partial\Omega,$$

where

$$(2.6) \quad h(V) = g(k(V), V) \quad \text{and} \quad U(x) = k(V(x)).$$

Regular stationary solutions appear to be unstable solutions to problem (1.1)-(1.4) under a simple assumption imposed on the first equation.

Theorem 2.1 (Instability of regular solutions). *Let (U, V) be a regular solution of problem (2.1)-(2.3) satisfying the following “autocatalysis condition”:*

$$(2.7) \quad f_u(U(x), V(x)) > 0 \quad \text{for all } x \in \overline{\Omega}.$$

Then, (U, V) is an unstable solution the initial-boundary value problem (1.1)-(1.4).

Inequality (2.7) can be interpreted as an autocatalysis in the dynamics of u at the steady state (U, V) . Notice that, in this work, the stability of a stationary solution is understood in the Lyapunov sense. Moreover, we prove the nonlinear instability of stationary solutions to problem (1.1)-(1.3) and not only their linear instability, *i.e.* the instability of zero solution of the corresponding linearized problem, see Section 4 for more explanations.

Each constant solution $(\bar{u}, \bar{v}) \in \mathbb{R}^2$ of problem (2.1)-(2.3) is a particular case of regular solutions. Thus, Theorem 2.1 provides a simple criterion for the diffusion-driven instability of (\bar{u}, \bar{v}) .

Corollary 2.2. *If a constant solution (\bar{u}, \bar{v}) of problem (1.1)-(1.4) (namely, $f(\bar{u}, \bar{v}) = 0$ and $g(\bar{u}, \bar{v}) = 0$) satisfies the inequalities*

$$(2.8) \quad f_u(\bar{u}, \bar{v}) > 0, \quad f_u(\bar{u}, \bar{v}) + g_v(\bar{u}, \bar{v}) < 0, \quad \det \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix} > 0,$$

then it has the DDI property.

This corollary results immediately from Theorem 2.1, because the second and the third inequality in (2.8) imply that (\bar{u}, \bar{v}) is stable under homogeneous perturbations, see Remark 5.2 below for more details.

Remark 2.3. The instability results from Theorem 2.1 and Corollary 2.2 can be summarized in the following way: This is a classical idea that, in a system of reaction-diffusion equations with a constant solution having the DDI property, one expects stable patterns to appear around that constant steady state. For the initial-boundary value problem

for reaction-diffusion-ODE system with a single diffusion equation (1.1)-(1.3), stationary solutions can be constructed in the case of several interesting models (see Section 3). However, the same mechanism which destabilizes constant solutions of such models, destabilizes also non-constant solutions.

We prove Theorem 2.1 in Section 4 by applying ideas invented for analysis of the Euler equation and other fluid dynamics models. In that approach, it suffices to show that the spectrum of the linearized operator

$$\mathcal{L} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} \equiv \begin{pmatrix} 0 \\ \Delta \tilde{v} \end{pmatrix} + \begin{pmatrix} f_u(U, V) & f_v(U, V) \\ g_u(U, V) & g_v(U, V) \end{pmatrix} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix}$$

with the Neumann boundary condition $\partial_\nu \tilde{v} = 0$, has so-called *spectral gap*, namely, there exists a subset of the spectrum $\sigma(\mathcal{L})$, which has a positive real part, separated from zero. Here, we prove that $\sigma(\mathcal{L}) \subset \mathbb{C}$ consists of the interval $\{f_u(U(x), V(x)) : x \in \overline{\Omega}\}$ and of isolated eigenvalues of \mathcal{L} , see Section 4 and, in particular, Fig. 4.1 for more details.

More precise description of $\sigma(\mathcal{L})$ is possible in the case of our model examples gathered in Section 3, where the autocatalysis condition (2.7) is satisfied, and moreover, the quantity $f_u(U(x), V(x))$ is independent of x for every regular stationary solution.

Corollary 2.4. *Let (U, V) be a regular solution of problem (2.1)-(2.3). Assume that there exists a constant $\lambda_0 > 0$ such that the following autocatalysis condition is satisfied:*

$$(2.9) \quad 0 < \lambda_0 = f_u(U(x), V(x)) \quad \text{for all } x \in \overline{\Omega}.$$

Suppose also the following “compensation condition” at the stationary solution (U, V)

$$(2.10) \quad g_u(U(x), V(x))f_v(U(x), V(x)) < 0 \quad \text{for all } x \in \overline{\Omega}.$$

Then, the spectrum $\sigma(\mathcal{L})$ contains the number λ_0 , which is an element of the continuous spectrum of \mathcal{L} and a sequence of real eigenvalues $\{\lambda_n\}_{n=1}^\infty$ of \mathcal{L} converging towards λ_0 .

In Section 3, we recall models from mathematical biology where both conditions: autocatalysis (2.7) and compensation (2.10) are fulfilled, which can be checked in a surprisingly simple way.

Remark 2.5. If one replaces the compensation condition (2.10) by the following one

$$(2.11) \quad g_u(U(x), V(x))f_v(U(x), V(x)) > 0 \quad \text{for all } x \in \overline{\Omega},$$

then the statement of Theorem 2.4 remains true, what can be proved by an obvious modification of the proof given in Section 4. However, below in Corollaries 2.14 and 2.15, we show that the compensation condition (2.10) has to be satisfied for reaction-diffusion-ODE problems which have constant solutions with the DDI property as well as non-constant stationary solutions.

The initial-boundary value problem (1.1)-(1.4) may also have non-regular steady states in the case when the equation $f(U, V) = 0$ is not uniquely solvable. Choosing different branches of solutions of the equation $f(U(x), V(x)) = 0$, we obtain the relation $U(x) = k(V(x))$ with a discontinuous, piecewise C^1 -function k . Here, we recall that a couple $(U, V) \in L^\infty(\Omega) \times W^{1,2}(\Omega)$ is a *weak solution* of problem (2.1)-(2.3) if the equation $f(U(x), V(x)) = 0$ is satisfied for almost all $x \in \Omega$ and if

$$-\int_{\Omega} \nabla V(x) \cdot \nabla \varphi(x) \, dx + \int_{\Omega} g(U(x), V(x)) \varphi(x) \, dx = 0$$

for all test functions $\varphi \in W^{1,2}(\Omega)$.

In this work, we do not prove the existence of such discontinuous solutions and we refer the reader to classical works [2, 19, 30] as well as to our recent paper [14, Thm. 2.9] for explanations how to construct such solutions to one dimensional problems using the phase portrait analysis. Our goal is to formulate a counterpart of the autocatalysis condition (2.7) which leads also to instability of weak (including discontinuous) stationary solutions.

The following two corollaries can be proved in the same way as Theorem 2.1.

Corollary 2.6. *Assume that (U, V) is a weak bounded solution of problem (2.1)-(2.3) satisfying the following counterpart of the autocatalysis condition*

$$(2.12) \quad \text{Range } f_u(U, V) \equiv \{f_u(U(x), V(x)) : x \in \overline{\Omega}\} \subset [\lambda_0, \Lambda_0]$$

for some constants $0 < \lambda_0 \leq \Lambda_0 < \infty$. Suppose, moreover, that there exists $x_0 \in \Omega$ such that $f_u(U, V)$ is continuous in a neighborhood of x_0 . Then, (U, V) is an unstable solution the initial-boundary value problem (1.1)-(1.4).

In fact, Theorem 2.1 is a particular case of Corollary 2.6, however, we prefer to state those two results separately to emphasize the role of the autocatalysis condition (2.7) in the proof of instability of stationary solutions.

The following corollary covers the case when the generalized autocatalysis condition (2.12) fails to hold.

Corollary 2.7 (Instability of weak solutions). *Assume that the nonlinear term in equation (1.1) satisfies $f(0, v) = 0$ for all $v \in \mathbb{R}$. Suppose that (U, V) is a weak bounded solution of problem (2.1)-(2.3) with the following property: there exist constants $0 < \lambda_0 < \Lambda_0 < \infty$ such that*

$$(2.13) \quad \lambda_0 \leq f_u(U(x), V(x)) \leq \Lambda_0 \quad \text{for all } x \in \Omega, \quad \text{where } U(x) \neq 0.$$

Suppose, moreover, that there exists $x_0 \in \Omega$ such that $U(x_0) \neq 0$ and that the functions $U = U(x)$ as well as $f_u(U, V)$ are continuous in a neighborhood of x_0 . Then, (U, V) is an unstable solution the initial-boundary value problem (1.1)-(1.4).

Remark 2.8. A typical nonlinearity satisfying the assumptions of Corollary 2.7 has the form $f(u, v) = r(u, v)u$ and appears in the models where the unknown variable u evolves according to the Malthusian law with a growth rate r depending on u and other variables of the model.

We defer the proofs of Theorems 2.1 and of Corollaries 2.4, 2.6, and 2.7 to Section 4.

2.2. Turing-type mechanism of pattern formation. Let us recall that, in initial-boundary value problems for reaction-diffusion equations modeling biological pattern formation,

$$(2.14) \quad u_t = \varepsilon \Delta u + f(u, v), \quad v_t = D \Delta v + g(u, v),$$

the nonlinearities are typically satisfying the inequalities $f_u > 0$ and $g_v < 0$. Then, the DDI phenomenon requires the condition $f_u g_v - f_v g_u > 0$, and therefore, f_v and g_u satisfy also the compensation condition $f_v g_u < 0$. Consequently, the signs of f_v and g_u should be opposite and there are only two possibilities

$$\begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} = \quad \text{either} \quad \begin{pmatrix} + & - \\ + & - \end{pmatrix} \quad \text{or} \quad \begin{pmatrix} + & + \\ - & - \end{pmatrix}.$$

The former on the right-hand side above is called an *activator-inhibitor* system, and the latter is a *resource-consumer* system. We refer the reader to the Murray books [21, 22]

and to the review article [33] as well as to references therein for more information on DDI in the case of two component reaction-diffusion systems and to the paper [31] in the case of several component systems. A detailed discussion of the DDI phenomena in the case of three component systems with some diffusion coefficients equal to zero can be found in the recent work [1].

Our next goal is to show that the autocatalysis inequality $f_u > 0$ and the compensation inequality $f_v g_u < 0$ at a stationary solution (*cf.* the assumptions of Corollary 2.4) appear indeed in system (2.14) with $\varepsilon = 0$ exhibiting DDI if there exist spatially heterogeneous stationary solutions.

Since it is natural to expect the existence of such steady states in models based on the Turing idea, let us first state a simple but fundamental property of stationary solutions to (1.1)-(1.4).

Proposition 2.9. *Assume that (U, V) is a non-constant regular solution of stationary problem (2.1)-(2.3). Then, there exists $x_0 \in \overline{\Omega}$, such that vector $(\bar{u}, \bar{v}) \equiv (U(x_0), V(x_0))$ is a constant solution of problem (2.1)-(2.3).*

The proof of Proposition 2.9 is short. It suffices to integrate equation (2.2) over Ω and to use the Neumann boundary condition (2.3) to obtain $\int_{\Omega} g(U(x), V(x)) dx = 0$. Hence, there exists $x_0 \in \overline{\Omega}$ such that $g(U(x_0), V(x_0)) = 0$, because U and V are continuous. Thus, by equation (2.1), we also have $f(U(x_0), V(x_0)) = 0$.

Next, we formulate our standing assumption on constant solutions. In this work, we consider only *non-degenerate* constant stationary solution (\bar{u}, \bar{v}) of the reaction-diffusion-ODE system (1.1)-(1.3), vectors *i.e.* (\bar{u}, \bar{v}) satisfying $f(\bar{u}, \bar{v}) = 0$ and $g(\bar{u}, \bar{v}) = 0$. It means

$$(2.15) \quad f_u(\bar{u}, \bar{v}) + g_v(\bar{u}, \bar{v}) \neq 0, \quad \det \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix} \neq 0, \quad \text{and} \quad f_u(\bar{u}, \bar{v}) \neq 0.$$

Notice that the first two conditions in (2.15) allow us to study the asymptotic stability of (\bar{u}, \bar{v}) as a solution to the corresponding kinetic system of ordinary differential equations

$$(2.16) \quad \frac{du}{dt} = f(u, v), \quad \frac{dv}{dt} = g(u, v),$$

by analyzing eigenvalues of the corresponding linearization matrix, see Remark 5.2 below for more details. On the other hand, by last condition in (2.15), the equation $f(U, V) = 0$ can be uniquely solved with respect to U in the neighborhood of (\bar{u}, \bar{v}) .

In the case described by Proposition 2.9, we say that *a non-constant solution (U, V) touches a constant solution (\bar{u}, \bar{v})* . Now, we prove an important property of the constant solutions which are touched by non-constant solutions, and, for simplicity of the exposition, we limit our study to regular solutions.

Theorem 2.10. *Let $(U(x), V(x))$ be a regular stationary solution of problem (1.1)-(1.3) and assume that all constant stationary solutions which are touched by (U, V) , are non-degenerate (*cf.* (2.15)). Then, at least at one of those constant solutions, denoted here by (\bar{u}, \bar{v}) , the following inequality holds*

$$(2.17) \quad \frac{1}{f_u(\bar{u}, \bar{v})} \det \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix} > 0.$$

The proof of Theorem 2.10 is based on properties of solutions to the elliptic Neumann problem (2.4)-(2.5) (see Theorem 5.1, below) and we present it in Section 5.

Now, let us derive properties of a constant solution (\bar{u}, \bar{v}) which satisfies inequality (2.17).

Remark 2.11. One should notice in the following corollaries that we do not impose the autocatalysis condition (2.7) to prove the instability of a constant steady state. Here, this condition is a consequence of the fact that the constant solution (\bar{u}, \bar{v}) is touched by a non-constant solution and because (\bar{u}, \bar{v}) satisfies inequality (2.17).

Corollary 2.12. *Denote by (\bar{u}, \bar{v}) a non-degenerate constant solution of problem (1.1)-(1.4), which satisfies inequality (2.17). Then, we have the following alternative:*

- *either (\bar{u}, \bar{v}) is the constant solution of the reaction-diffusion-ODE system (1.1)-(1.4) with the DDI property,*
- *or (\bar{u}, \bar{v}) is an unstable solution of the kinetic system (2.16).*

In the example discussed in Subsection 3.2, we show that both cases from Corollary 2.12 can indeed occur in one model, depending on its parameters.

Now, we have to emphasize the following *necessary condition* for the DDI property, which is obtained immediately from Corollary 2.12.

Corollary 2.13. *If problem (1.1)-(1.4) has only one constant solution (\bar{u}, \bar{v}) which is asymptotically stable as a solution to kinetic system (2.16) and if there exists a nonconstant regular stationary solution which touches (\bar{u}, \bar{v}) , then the constant steady state (\bar{u}, \bar{v}) is an unstable solutions of (1.1)-(1.4) (thus, (\bar{u}, \bar{v}) has the DDI property).*

Next, we discuss the compensation condition (2.10) to link Theorem 2.10 with the the assumptions of Corollary 2.4.

Corollary 2.14. *Let (\bar{u}, \bar{v}) be a constant solution of problem (1.1)-(1.4) satisfying inequality (2.17). If (\bar{u}, \bar{v}) is an asymptotically stable solution to kinetic system (2.16), then it satisfies the compensation inequality $f_v(\bar{u}, \bar{v})g_u(\bar{u}, \bar{v}) < 0$.*

Thus, we obtain the following local version of the compensation assumption (2.10) for a regular non-constant stationary solution.

Corollary 2.15. *Let (U, V) be a non-constant regular stationary solution of problem (1.1)-(1.4). Denote by (\bar{u}, \bar{v}) a constant solution which is touched by (U, V) and which satisfies inequality (2.17). Assume that (\bar{u}, \bar{v}) is an asymptotically stable solution of kinetic system (2.16). Then, there exists $x_0 \in \Omega$ such that $f_v(U(x_0), V(x_0))g_u(U(x_0), V(x_0)) < 0$.*

In other words, every non-constant solution $(U(x), V(x))$ which touches a constant solution with the DDI property has to satisfy compensation property (2.10) at least at the point x_0 and, by continuity, in a neighborhood of x_0 . Notice, however, that we require this condition in Corollary 2.4 to be satisfied for all $x \in \bar{\Omega}$.

3. MODEL EXAMPLES

In this section, our results are illustrated by applying them to nonlinearities from mathematical biology.

3.1. Gray-Scott model. Instability phenomena described in Section 2 appear, for example, in the following initial-boundary value problem with nonlinearities as in the celebrated Gray-Scott system describing pattern formation in chemical reactions [7]

$$(3.1) \quad u_t = -(B + k)u + u^2v \quad \text{for } x \in \bar{\Omega}, t > 0,$$

$$(3.2) \quad v_t = \Delta v - u^2v + B(1 - v) \quad \text{for } x \in \Omega, t > 0,$$

where B and k are positive constants, with the zero-flux boundary condition for v and with nonnegative initial conditions. Here, every regular positive stationary solution (U, V) of the Neumann boundary-initial value problem for equations (3.1)-(3.2) has to satisfy the relation $U = (B + k)/V$, hence,

$$(3.3) \quad \Delta V - BV - \frac{(B + k)^2}{V} + B = 0 \quad \text{for } x \in \Omega,$$

$$(3.4) \quad \partial_\nu V = 0 \quad \text{for } x \in \partial\Omega.$$

All continuous positive solutions of such boundary value problem in one dimensional case have been constructed in our recent paper [14, Sec. 5]. A construction of discontinuous stationary solutions to the reaction-diffusion-ODE problem for (3.1)-(3.2) can be also found in [14, Thm. 2.9].

Our instability results, formulated in Section 2.1, implicate that all stationary solutions (constant, regular as well as discontinuous) of the reaction-diffusion-ODE problem for equations (3.1)-(3.2) are unstable under heterogeneous perturbations. For the proof, it suffices to notice that the autocatalysis assumption (2.7) holds true because, for $U = (B + k)/V$, the function $f_u(U(x), V(x))$ is independent of x and satisfies

$$\lambda_0 = f_u(U(x), V(x)) = -(B + k) + 2U(x)V(x) = B + k > 0 \quad \text{for all } x \in \Omega.$$

This is the case of nonlinearities to which one can apply Corollary 2.1, because the compensation assumption (2.10) at a positive solution (U, V) is also valid due to the following calculation $f_v(U, V) \cdot g_u(U, V) = -2U^3V < 0$ for all positive stationary solutions.

Now, it suffices to apply either Theorem 2.1 or Corollary 2.4.

3.2. Activator-inhibitor system. Now, we consider the following activator-inhibitor system with no diffusion of activator

$$(3.5) \quad u_t = -u + \frac{u^p}{v^q} \quad \text{for } x \in \overline{\Omega}, t > 0,$$

$$(3.6) \quad \tau v_t = \Delta v - v + \frac{u^r}{v^s} \quad \text{for } x \in \Omega, t > 0,$$

supplemented with positive initial data and with the zero-flux boundary condition for $v = v(x, t)$. We assume that $\tau > 0$ and exponents satisfy $p > 1$, $q, r > 0$ and $s \geq 0$. Such nonlinearities were proposed by Gierer and Meinhardt [6] to describe a system consisting of a slowly diffusing activator and a rapidly diffusing inhibitor. In their model, a high concentration of activator is supposed to induce morphogenetic changes in a biological tissue.

First, we observe that every positive regular stationary solution satisfies the relation $U^{p-1} = V^q$, thus, the function $V = V(x)$ is a solution of the boundary value problem

$$(3.7) \quad \Delta V - V + V^Q = 0 \quad \text{for } x \in \Omega,$$

$$(3.8) \quad \partial_\nu V = 0 \quad \text{for } x \in \partial\Omega,$$

where $Q = qr/(p-1) - s$. This problem with $Q > 1$ was considered in a series of papers, *e.g.* [35, 11, 25, 26]. In particular, when $1 < Q < \frac{N+2}{N-2}$ for $N \geq 3$, and $1 < Q < \infty$ for $N = 1, 2$, it was shown that it has a positive solution V for a sufficiently large domain Ω . We refer the reader to the review article [23] for more comments and references on this problem.

Here, the autocatalysis condition (2.7) holds true for regular stationary solutions of system (3.5)-(3.6), because

$$f_u(U, V) = -1 + p \frac{U^{p-1}}{V^q} = -1 + p > 0 \quad \text{for } U^{p-1} = V^q.$$

Notice that $\lambda_0 = f_u(U(x), V(x))$ is independent of x , as required in Corollary 2.4. Next, we check directly the compensation assumption (2.10)

$$f_v(U, V) \cdot g_u(U, V) = \left(-q \frac{U^p}{V^{q+1}}\right) \left(r \frac{U^{r-1}}{V^s}\right) = -rq \frac{U^{p+r-1}}{V^{s+q+1}} < 0 \quad \text{for all } x \in \overline{\Omega},$$

for every positive stationary solution (U, V) . As a consequence either of Theorem 2.1 or of Corollary 2.4, we obtain that all positive regular stationary solutions to system (3.5)-(3.6) with the Neumann boundary condition for v are unstable.

By Proposition 2.9, every regular stationary solution of the Neumann boundary-initial value problem for system (3.5)-(3.6) has to touch the only constant positive solution $(\bar{u}, \bar{v}) = (1, 1)$ of system (3.5)-(3.6). In the case of the kinetic system corresponding to (3.5)-(3.6), it is shown in [24] that this constant solution is

- (1) asymptotically stable if the parameter $\tau > 0$ is small;
- (2) unstable if the parameter $\tau > 0$ is large.

Thus, by Corollary 2.12, the constant solution $(\bar{u}, \bar{v}) = (1, 1)$ of the reaction-diffusion-ODE system (3.5)-(3.6) with small $\tau > 0$, has the DDI property.

3.3. Model of early carcinogenesis. The main motivation for the research reported in this work comes from our studies of the reaction-diffusion system of three ordinary/partial differential equations modeling the diffusion-regulated growth of a cell population of the following form

$$(3.9) \quad u_t = \left(\frac{av}{u+v} - d_c\right)u \quad \text{for } x \in \overline{\Omega}, t > 0,$$

$$(3.10) \quad v_t = -d_b v + u^2 w - dv \quad \text{for } x \in \overline{\Omega}, t > 0,$$

$$(3.11) \quad w_t = D\Delta w - d_g w - u^2 w + dv + \kappa_0 \quad \text{for } x \in \Omega, t > 0,$$

supplemented with zero-flux boundary conditions for the function w and with nonnegative initial conditions, [14]. Here, the letters $a, d_c, d_b, d_g, d, D, \kappa_0$ denote positive constants.

In the present paper, we focus on a reduced two-equation version of model (3.9)-(3.11), obtained by quasi-steady state approximation of the dynamics of v . Applying the quasi-steady state approximation in equation (3.10) (namely, assuming that $v_t \equiv 0$), we obtain the relation $v = u^2 w / (d_b + d)$, which after substituting into remaining equations (3.9) and (3.11) yields the following initial-boundary value problem for the reaction-diffusion-ODE system

$$(3.12) \quad u_t = \left(\frac{auw}{1+uw} - d_c\right)u \quad \text{for } x \in \overline{\Omega}, t > 0,$$

$$(3.13) \quad w_t = D\Delta w - d_g w - \frac{d_b}{d_b + d} u^2 w + \kappa_0 \quad \text{for } x \in \Omega, t > 0.$$

Here, the autocatalysis assumption (2.9) and the compensation assumption (2.10) are satisfied by simple calculations, which are analogous to those in previous examples. As a consequence, all nonnegative stationary solutions of system (3.12)-(3.13) are unstable due to Theorem 2.1 and Corollary 2.7. This gives a counterpart of our results on three equation model (3.9)-(3.11) proved in [14].

Numerical simulations suggest that the two-equation model exhibits qualitatively the same dynamics as (3.9)-(3.11). A rigorous derivation of the two equation model (3.12)-(3.13) from the model (3.9)-(3.11) as well as other properties of solutions to (3.12)-(3.13) are presented in Appendix A of this work. Our detailed studies of stability properties of space homogeneous solutions of the two equation model (3.12)-(3.13) are reported in Appendix B. In particular, by Corollary 2.12, constant steady states of (3.12)-(3.13) are either unstable solutions of the corresponding kinetic system or they have the DDI property.

4. INSTABILITY OF STATIONARY SOLUTIONS

4.1. Existence of solutions. We begin our study of properties of solutions to the initial-boundary value problem (1.1)–(1.4) by recalling the results on local-in-time existence and uniqueness of solutions for all bounded initial conditions.

Theorem 4.1 (Local-in-time solution). *Assume that $u_0, v_0 \in L^\infty(\Omega)$. Then, there exists $T = T(\|u_0\|_\infty, \|v_0\|_\infty) > 0$ such that the initial-boundary value problem (1.1)–(1.4) has a unique local-in-time mild solution $u, v \in L^\infty([0, T], L^\infty(\Omega))$.*

We recall that a mild solution of problem (1.1)–(1.4) is a couple of measurable functions $u, v : [0, T] \times \overline{\Omega} \mapsto \mathbb{R}$ satisfying the following system of integral equations

$$(4.1) \quad u(x, t) = u_0(x) + \int_0^t f(u(x, s), v(x, s)) ds,$$

$$(4.2) \quad v(x, t) = e^{t\Delta} v_0(x) + \int_0^t e^{(t-s)\Delta} g(u(x, s), v(x, s)) ds,$$

where $e^{t\Delta}$ is the semigroup of linear operators generated by Laplacian with the Neumann boundary condition. Since our nonlinearities $f = f(u, v)$ and $g = g(u, v)$ are locally Lipschitz continuous, to construct a local-in-time unique solution of system (4.1)–(4.2), it suffices to apply the Banach fixed point theorem. Details of such a reasoning and the proof of Theorem 4.1 in a case of much more general systems of reaction-diffusion equations can be found in [29, Thm. 1, p. 111], see also our recent work [14, Ch. 3] for a construction of nonnegative solutions of particular reaction-diffusion-ODE problems.

Remark 4.2. If u_0 and v_0 are more regular, *i.e.* if for some $\alpha \in (0, 1)$ we have $u_0 \in C^\alpha(\overline{\Omega})$, $v_0 \in C^{2+\alpha}(\overline{\Omega})$ and $\partial_\nu v_0 = 0$ on $\partial\Omega$, then the mild solution of problem (1.1)–(1.4) is smooth and satisfies $u \in C^{1,\alpha}([0, T] \times \overline{\Omega})$ and $v \in C^{1+\alpha/2, 2+\alpha}([0, T] \times \overline{\Omega})$. We refer the reader to [29, Thm. 1, p. 112] as well as to [5] for studies of general reaction-diffusion-ODE systems in the Hölder spaces.

4.2. General instability result. The next goal in this section is to show that, under appropriate conditions, linear instability of stationary solutions of a reaction-diffusion-ODE problem implies their nonlinear instability. Such a theorem is well-known for ordinary differential equations. Furthermore, in the case of reaction-diffusion equations, one can apply the abstract result from the book by Henry [8, Thm. 5.1.3]. However, in the case of reaction-diffusion-ODE problems, we often encounter discontinuous stationary solutions and the corresponding linearization operator may have a non-empty continuous spectrum. Hence, checking the assumptions of the general result from [8] does not seem to be straightforward.

Therefore, we propose here a different approach which was developed to study stability of stationary solutions of fluid dynamic equations [10, 4], using the, so-called, *linearization*

principle. In that setting, only the existence of a spectral gap of a linearization operator is required to show the instability of steady states. This classical method has been recently recalled by Mulone and Solonnikov [20] to show the instability of regular stationary solutions to certain reaction-diffusion-ODE problems, however, assumptions imposed in [20] are not satisfied in our case.

The crucial idea underlying this approach is to use two Banach spaces: a “large” space Z where the spectrum of a linearization operator is studied and a “small” space $X \subset Z$ where an existence of solutions can be proved.

Remark 4.3. To study instability properties of solutions to the reaction-diffusion-ODE problem (1.1)–(1.4), we use $X = L^\infty(\Omega) \times L^\infty(\Omega)$ and $Z = L^2(\Omega) \times L^2(\Omega)$ for a bounded domain $\Omega \subset \mathbb{R}^N$, supplemented with the usual norms.

Let us consider a general evolution equation

$$(4.3) \quad w_t = \mathcal{L}w + \mathcal{N}(w), \quad w(0) = w_0$$

where \mathcal{L} is a generator of a C_0 -semigroup of linear operators $\{e^{t\mathcal{L}}\}_{t \geq 0}$ on a Banach space Z and \mathcal{N} is a nonlinear operator such that $\mathcal{N}(0) = 0$.

Definition 4.4. Let (X, Z) be a pair of Banach spaces such that $X \subset Z$ with a dense and continuous embedding. A solution $w \equiv 0$ of the Cauchy problem (4.3) is called (X, Z) -nonlinearly stable if for every $\varepsilon > 0$, there exists $\delta > 0$ so that if $w(0) \in X$ and $\|w(0)\|_Z < \delta$, then

- (1) there exists a global in time solution to (4.3) such that $w \in C([0, \infty); X)$;
- (2) $\|w(t)\|_Z < \varepsilon$ for all $t \in [0, \infty)$.

An equilibrium $w \equiv 0$ that is not stable (in the above sense) is called *Lyapunov unstable*.

In this work, we drop the reference to the pair (X, Z) . Let us also note that, under this definition of stability, a loss of the existence of a solution to (4.3) is a particular case of instability.

Now, we recall a result linking the existence of the so-called *spectral gap* to the nonlinear instability of a trivial solution to problem (4.3).

Theorem 4.5. We impose the two following assumptions.

- The semigroup of linear operators $\{e^{t\mathcal{L}}\}_{t \geq 0}$ on Z satisfies “the spectral gap condition”, namely, we suppose that for every $t > 0$ the spectrum σ of the linear operator $e^{t\mathcal{L}}$ can be decomposed as follows: $\sigma = \sigma(e^{t\mathcal{L}}) = \sigma_- \cup \sigma_+$ with $\sigma_+ \neq \emptyset$, where

$$\sigma_- \subset \{z \in \mathbb{C} : e^{\kappa t} < |z| < e^{\mu t}\} \quad \text{and} \quad \sigma_+ \subset \{z \in \mathbb{C} : e^{Mt} < |z| < e^{\Lambda t}\}$$

and

$$-\infty \leq \kappa < \mu < M < \Lambda < \infty \quad \text{for some } M > 0.$$

- The nonlinear term \mathcal{N} satisfies the inequality

$$(4.4) \quad \|\mathcal{N}(w)\|_Z \leq C_0 \|w\|_X \|w\|_Z \quad \text{for all } w \in X \text{ satisfying } \|w\|_X < \rho$$

for some constants $C_0 > 0$ and $\rho > 0$.

Then, the trivial solution $w_0 \equiv 0$ of the Cauchy problem (4.3) is nonlinearly unstable.

The proof of this theorem can be found in the work by Friedlander *et al.* [4, Thm. 2.1].

Remark 4.6. The operator \mathcal{L} considered in this work satisfies the “spectral mapping theorem”: $\sigma(e^{t\mathcal{L}}) \setminus \{0\} = e^{t\sigma(\mathcal{L})}$, see Lemma 4.8, below. Thus, due to the relation $|e^z| = e^{\operatorname{Re} z}$ for every $z \in \mathbb{C}$, the spectral gap condition required in Theorem 4.5 holds true if for every $\lambda \in \sigma(\mathcal{L})$, either $\operatorname{Re} \lambda \in (\kappa, \mu)$ or $\operatorname{Re} \lambda \in (M, \Lambda)$.

Remark 4.7. The authors of the reference [4, Thm. 2.1] formulated their instability result under the spectral gap condition for a *group* of linear operators $\{e^{t\mathcal{L}}\}_{t \in \mathbb{R}}$ and in the case of a finite constant κ (caution: in [4], the letter λ is used instead of κ). However, the proof of [4, Thm. 2.1] holds true (with a minor and obvious modification) in the case of a semigroup $\{e^{t\mathcal{L}}\}_{t \geq 0}$ as well as $\kappa = -\infty$ is allowed, as stated in Theorem 4.5. This extension is important to deal with the operator \mathcal{L} introduced in Lemma 4.8 below, which generates a semigroup of linear operators, only, and which may have an unbounded sequence of eigenvalues. We refer the reader also to the paper [32] for another instability result under less restrictive assumption on the spectrum of an operator \mathcal{L} , but for a smaller class of nonlinearities.

4.3. Linearization of reaction-diffusion-ODE problems. Let (U, V) be a stationary solution of problem (1.1)-(1.4). Substituting

$$u = U + \tilde{u} \quad \text{and} \quad v = V + \tilde{v}$$

into (1.1)-(1.2) we obtain the initial-boundary value problem for the perturbation (\tilde{u}, \tilde{v}) of the form (4.3):

$$(4.5) \quad \frac{\partial}{\partial t} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} = \mathcal{L} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} + \mathcal{N} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix},$$

with the Neumann boundary condition, $\partial_\nu \tilde{v} = 0$, where the linear operator \mathcal{L} and the nonlinearity \mathcal{N} are defined and studied in the following two lemmas.

Lemma 4.8. *Let (U, V) be a bounded (not necessarily regular) stationary solution of problem (1.1)-(1.4). We consider the following linear system*

$$(4.6) \quad \begin{pmatrix} \tilde{u}_t \\ \tilde{v}_t \end{pmatrix} = \mathcal{L} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} \equiv \begin{pmatrix} 0 \\ \Delta \tilde{v} \end{pmatrix} + \begin{pmatrix} f_u(U, V) & f_v(U, V) \\ g_u(U, V) & g_v(U, V) \end{pmatrix} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix}$$

with the Neumann boundary condition $\partial_\nu \tilde{v} = 0$. Then, the operator \mathcal{L} with the domain $D(\mathcal{L}) = L^2(\Omega) \times W^{2,2}(\Omega)$ generates an analytic semigroup $\{e^{t\mathcal{L}}\}_{t \geq 0}$ of linear operators on $L^2(\Omega) \times L^2(\Omega)$, which satisfies “the spectral mapping theorem”:

$$(4.7) \quad \sigma(e^{t\mathcal{L}}) \setminus \{0\} = e^{t\sigma(\mathcal{L})} \quad \text{for every } t \geq 0.$$

Proof. Notice that \mathcal{L} is a bounded perturbation of the operator

$$\mathcal{L}_0 \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} \equiv \begin{pmatrix} 0 \\ \Delta \tilde{v} \end{pmatrix}$$

with the Neumann boundary condition for \tilde{v} and with the domain $D(\mathcal{L}_0) = L^2(\Omega) \times W^{2,2}(\Omega)$, which generates an analytic semigroup on $L^2(\Omega) \times L^2(\Omega)$. Thus, it is well-known (see e.g. [3, Ch. III.1.3]) that the same property holds true for \mathcal{L} .

“The spectral mapping theorem” for the semigroup $\{e^{t\mathcal{L}}\}_{t \geq 0}$ expressed by equality (4.7) holds true if the semigroup is e.g. eventually norm-continuous (see [3, Ch. IV.3.10]). Since every analytic semigroup of linear operators is eventually norm-continuous, we obtain immediately relation (4.7) (cf. [3, Ch. IV, Corollary 3.12]). \square

Next, we show that the nonlinearity in equation (4.5) satisfies the assumption (4.4) from Theorem 4.5.

Lemma 4.9. *Let (U, V) be a bounded (not necessarily regular) stationary solution of problem (1.1)-(1.4). Then, the nonlinear operator*

$$\mathcal{N} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} \equiv \begin{pmatrix} f(U + \tilde{u}, V + \tilde{v}) - f(U, V) \\ g(U + \tilde{u}, V + \tilde{v}) - g(U, V) \end{pmatrix} - \begin{pmatrix} f_u(U, V) & f_v(U, V) \\ g_u(U, V) & g_v(U, V) \end{pmatrix} \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix}$$

satisfies

$$\begin{aligned} \|\mathcal{N}(\tilde{u}, \tilde{v})\|_{L^2 \times L^2} &\leq C(\rho, \|U\|_{L^\infty}, \|V\|_{L^\infty})(\|\tilde{u}\|_{L^\infty} + \|\tilde{v}\|_{L^\infty})(\|\tilde{u}\|_{L^2} + \|\tilde{v}\|_{L^2}) \\ &= C(\rho, \|U\|_{L^\infty}, \|V\|_{L^\infty})\|(\tilde{u}, \tilde{v})\|_{L^\infty \times L^\infty}\|(\tilde{u}, \tilde{v})\|_{L^2 \times L^2} \end{aligned}$$

for all $\tilde{u}, \tilde{v} \in L^\infty$ such that $\|\tilde{u}\|_{L^\infty} < \rho$ and $\|\tilde{v}\|_{L^\infty} < \rho$, where $\rho > 0$ is an arbitrary constant.

Proof. This is nothing but the Taylor formula applied to the C^2 -nonlinearities $f = f(u, v)$ and $g = g(u, v)$ in problem (1.1)-(1.2). \square

4.4. Instability of steady states. Now, we are in a position to apply the described above general theory to show the instability of stationary solutions to reaction-diffusion-ODE problems.

Proof of Theorem 2.1. Let $(U(x), V(x))$ be a regular stationary solution to problem (1.1)-(1.4). To show its instability, in view of Theorem 4.5 combined with Lemmas 4.8 and 4.9, it suffices to study the spectrum $\sigma(\mathcal{L})$ of the linear operator \mathcal{L} defined formally by formula (4.6) with the domain $D(\mathcal{L}) = L^2(\Omega) \times W^{2,2}(\Omega)$.

Let us define the constants

$$(4.8) \quad \lambda_0 = \inf_{x \in \overline{\Omega}} f_u(U(x), V(x)) > 0 \quad \text{and} \quad \Lambda_0 = \sup_{x \in \overline{\Omega}} f_u(U(x), V(x)) > 0,$$

where the positivity of λ_0 is a consequence of the autocatalysis condition (2.7). We are going to prove that $\sigma(\mathcal{L}) \subset \mathbb{C}$ consists of all numbers from the interval $[\lambda_0, \Lambda_0]$ and of a set of (possibly complex) eigenvalues of $(\mathcal{L}, D(\mathcal{L}))$ which are isolated points of \mathbb{C} .

Part I: Interval $[\lambda_0, \Lambda_0]$. First, we show that for each $\lambda \in [\lambda_0, \Lambda_0]$ the operator

$$\mathcal{L} - \lambda I : L^2(\Omega) \times W^{2,2}(\Omega) \rightarrow L^2(\Omega) \times L^2(\Omega)$$

defined by formula

$$(\mathcal{L} - \lambda I)(\varphi, \psi) = ((f_u - \lambda)\varphi + f_v\psi, \Delta\psi + g_u\varphi + (g_v - \lambda)\psi),$$

where $f_u = f_u(U(x), V(x))$, etc., cannot have a bounded inverse. Suppose, *a contrario*, that $(\mathcal{L} - \lambda I)^{-1}$ exists and is bounded. Then, for a constant $K = \|(\mathcal{L} - \lambda I)^{-1}\|$, we have

$$\|(\varphi, \psi)\|_{L^2(\Omega) \times W^{2,2}(\Omega)} \leq K \|(\mathcal{L} - \lambda I)(\varphi, \psi)\|_{L^2(\Omega) \times L^2(\Omega)}$$

for all $(\varphi, \psi) \in L^2(\Omega) \times W^{2,2}(\Omega)$ or, equivalently, using the usual norms in $L^2(\Omega) \times W^{2,2}(\Omega)$ and in $L^2(\Omega) \times L^2(\Omega)$:

$$(4.9) \quad \begin{aligned} &\|\varphi\|_{L^2(\Omega)} + \|\psi\|_{W^{2,2}(\Omega)} \\ &\leq K (\|(f_u - \lambda)\varphi + f_v\psi\|_{L^2(\Omega)} + \|\Delta\psi + g_u\varphi + (g_v - \lambda)\psi\|_{L^2(\Omega)}). \end{aligned}$$

A contradiction will be obtained by showing that inequality (4.9) cannot be true for all $(\varphi, \psi) \in L^2(\Omega) \times W^{2,2}(\Omega)$.

To prove this claim, first we observe that, for each $\lambda \in [\lambda_0, \Lambda_0]$, there exists $x_0 \in \overline{\Omega}$ such that $f_u(U(x_0), V(x_0)) - \lambda = 0$. Hence, for every $\varepsilon > 0$ there is a ball $B_\varepsilon \subset \Omega$ such that $\|f_u - \lambda\|_{L^\infty(B_\varepsilon)} \leq \varepsilon$.

Next, for arbitrary $\psi \in C_c^\infty(\Omega)$ such that $\text{supp } \psi \subset B_\varepsilon$, we choose $\varphi \in L^2(\Omega)$ such that $\text{supp } \varphi \subset B_\varepsilon$ and in such a way that $\Delta\psi + g_u\varphi + (g_v - \lambda)\psi = \zeta$, where the function $\zeta \in L^2(\Omega)$ satisfies $\|\zeta\|_{L^2(\Omega)} \leq \varepsilon\|\varphi\|_{L^2(\Omega)}$. Let us explain that such a choice of $\varphi, \zeta \in L^2(\Omega)$ is always possible. We cut g_u at the level ε in the following way

$$g_u^\varepsilon = g_u^\varepsilon(U(x), V(x)) \equiv \begin{cases} g_u(U(x), V(x)) & \text{if } |g_u(U(x), V(x))| > \varepsilon, \\ \varepsilon & \text{if } |g_u(U(x), V(x))| \leq \varepsilon. \end{cases}$$

Since, $\Delta\psi + g_u\varphi + (g_v - \lambda)\psi = \Delta\psi + g_u^\varepsilon\varphi + (g_v - \lambda)\psi + (g_u - g_u^\varepsilon)\varphi$, we may set

$$\varphi = \frac{-(\Delta\psi + (g_v - \lambda)\psi)}{g_u^\varepsilon} \in L^2(\Omega) \quad \text{and} \quad \zeta = -(g_u - g_u^\varepsilon)\varphi \in L^2(\Omega)$$

with $\|g_u - g_u^\varepsilon\|_{L^\infty(\Omega)} \leq \varepsilon$.

Now, noting that $\text{supp } \varphi \subset B_\varepsilon$, we obtain the inequality

$$\|(f_u - \lambda)\varphi\|_{L^2(\Omega)} \leq \|(f_u - \lambda)\|_{L^\infty(B_\varepsilon)}\|\varphi\|_{L^2(\Omega)} \leq \varepsilon\|\varphi\|_{L^2(\Omega)}.$$

Thus, substituting functions φ , ψ , and ζ into inequality (4.9), we obtain the estimate

$$\begin{aligned} & \|\varphi\|_{L^2(\Omega)} + \|\psi\|_{W^{2,2}(\Omega)} \\ (4.10) \quad & \leq K(\|(f_u - \lambda)\|_{L^\infty(B_\varepsilon)}\|\varphi\|_{L^2(\Omega)} + \|f_v\psi\|_{L^2(\Omega)} + \|\zeta\|_{L^2(\Omega)}) \\ & \leq K(2\varepsilon\|\varphi\|_{L^2(\Omega)} + \|f_v\|_{L^\infty(\Omega)}\|\psi\|_{L^2(\Omega)}). \end{aligned}$$

Hence, choosing $\varepsilon > 0$ in such a way that $2K\varepsilon \leq 1$ and compensating the term $2K\varepsilon\|\varphi\|_{L^2(\Omega)}$ on the right-hand side of inequality (4.10) by its counterpart on the left-hand side, we obtain the estimate $\|\psi\|_{W^{2,2}(\Omega)} \leq K\|f_v\|_{L^\infty(\Omega)}\|\psi\|_{L^2(\Omega)}$, which, obviously, cannot be true for all $\psi \in C_c^\infty(\Omega)$ such that $\text{supp } \psi \subset B_\varepsilon$. We have completed the proof that each $\lambda \in [\lambda_0, \Lambda_0]$ belongs to $\sigma(\mathcal{L})$.

Part II: Eigenvalues. In the next step, we show that the remainder of the spectrum of $(\mathcal{L}, D(\mathcal{L}))$ consists of a discrete set of eigenvalues $\{\lambda_n\}_{n=1}^\infty \subset \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, analyzing the corresponding resolvent equations

$$(4.11) \quad (f_u - \lambda)\varphi + f_v\psi = F \quad \text{in } \overline{\Omega}$$

$$(4.12) \quad \Delta\psi + g_u\varphi + (g_v - \lambda)\psi = G \quad \text{in } \Omega$$

$$(4.13) \quad \partial_\nu\psi = 0 \quad \text{on } \partial\Omega,$$

with arbitrary $F, G \in L^2(\Omega)$. Here, one should notice that for every $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, one can solve equation (4.11) with respect to φ . Thus, after substituting the resulting expression $\varphi = (F - f_v\psi)/(f_u - \lambda) \in L^2(\Omega)$ into (4.12), we obtain the boundary value problem

$$(4.14) \quad \Delta\psi + q(\lambda)\psi = p(\lambda) \quad \text{for } x \in \Omega,$$

$$(4.15) \quad \partial_\nu\psi = 0 \quad \text{for } x \in \partial\Omega,$$

where

$$(4.16) \quad q(\lambda) = q(x, \lambda) = -\frac{g_u f_v}{f_u - \lambda} + g_v - \lambda \quad \text{and} \quad p(\lambda) = p(x, \lambda) = G - \frac{g_u F}{f_u - \lambda}.$$

For a fixed $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, by the Fredholm alternative, either the inhomogeneous problem (4.14)-(4.15) has a unique solution (so, λ is not an element of $\sigma(\mathcal{L})$) or else the

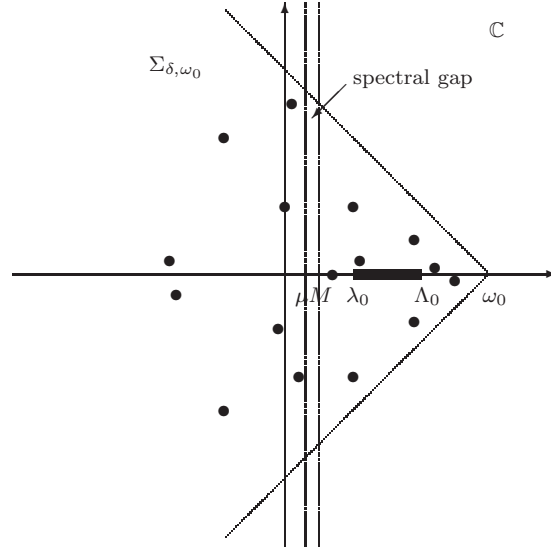


FIGURE 4.1. The spectrum $\sigma(\mathcal{L})$ is marked by thick dots and by the interval $[\lambda_0, \Lambda_0]$ in the sector $\Sigma_{\delta, \omega_0}$. The spectral gap is represented by the strip $\{\lambda \in \mathbb{C} : \mu \leq \operatorname{Re} \lambda \leq M\}$ without elements of $\sigma(\mathcal{L})$.

homogeneous boundary value problem

$$(4.17) \quad \Delta \psi + q(\lambda) \psi = 0 \quad \text{for } x \in \Omega,$$

$$(4.18) \quad \partial_\nu \psi = 0 \quad \text{for } x \in \partial\Omega,$$

has a nontrivial solution ψ . Hence, it suffices to consider those $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, for which problem (4.17)-(4.18) has nontrivial solution.

Now, we prove that the set $\sigma(\mathcal{L}) \setminus [\lambda_0, \Lambda_0]$ consists of isolated eigenvalues of \mathcal{L} , only. First, we rewrite problem (4.17)-(4.18) in the form

$$\psi = G[-(q(\lambda) + \ell)\psi] \equiv R(\lambda)\psi,$$

where the operator $G = “(\Delta - \ell I)^{-1}”$ supplemented with the Neumann boundary conditions is defined in the usual way. Here, $\ell \in \mathbb{R}$ is a fixed number different from each eigenvalue of Laplacian with the Neumann boundary condition.

Recall that, for each $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, the operator $R(\lambda) : L^2(\Omega) \rightarrow L^2(\Omega)$ is compact as the superposition of the compact operator G and of the continuous multiplication operator with the function $q(\lambda) + \ell \in L^\infty(\Omega)$. Moreover, the mapping $\lambda \mapsto R(\lambda)$ from the open set $\mathbb{C} \setminus [\lambda_0, \Lambda_0]$ into the Banach space of linear compact operators is analytic, which can be easily seen using the explicit form of $q(\lambda)$ in (4.16). Thus, the set $\sigma(\mathcal{L}) \setminus [\lambda_0, \Lambda_0]$ consists of isolated points due to the analytic Fredholm theorem (see Theorem 4.11, below). Here, to exclude the case (a) in Theorem 4.11, we have to show that the operator $I - R(\lambda)$ is invertible for some $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$. This is, however, the consequence of the fact that the inhomogeneous boundary value problem (4.14)-(4.15) has a unique solution if $\lambda > 0$ is chosen so large that $q(x, \lambda) < 0$.

Part III: Spectral gap. By Lemma 4.8, there exists a number $\omega_0 \geq 0$ such that the operator $(\mathcal{L} - \omega_0 I, D(\mathcal{L}))$ generates a bounded analytic semigroup on $L^2(\Omega) \times L^2(\Omega)$,

hence, this is a sectorial operator, see [3, Ch. II, Thm. 4.6]. In particular, there exists $\delta \in (0, \pi/2]$ such that $\sigma(\mathcal{L}) \subset \Sigma_{\delta, \omega_0} \equiv \{\lambda \in \mathbb{C} : |\arg(\lambda - \omega_0)| \geq \pi/2 + \delta\}$, see Fig. 4.1. The part of the spectrum $\sigma(\mathcal{L})$ in the triangle $\Sigma_{\delta, \omega_0} \cap \{\lambda \in \mathbb{C} : \operatorname{Re} \lambda > 0\}$ consists of all numbers from the interval $[\lambda_0, \Lambda_0]$ with $\lambda_0 > 0$ and of a discrete sequence of eigenvalues with accumulation points from the interval $[\lambda_0, \Lambda_0]$, only. Thus, we can easily find infinitely many $0 \leq \mu < M \leq \lambda_0$, for which the spectrum $\sigma(\mathcal{L})$ can be decomposed as required in Theorem 4.5. Here, one should use the spectral mapping theorem, *i.e.* equality (4.7), and Remark 4.6. \square

Remark 4.10. One should emphasize here that the instability of steady states from Theorem 2.1 is caused not by an eigenvalue with a positive real part, but rather by positive numbers from the interval $[\lambda_0, \Lambda_0]$ which are, in some cases, elements of continuous spectrum of the operator $(\mathcal{L}, D(\mathcal{L}))$, see Corollary 2.4.

The following general result on a family of compact operators was used in the proof of Theorem 2.1. We state it here for reader's convenience and its proof can be found in the Reed and Simon book [28, Thm. VI.14].

Theorem 4.11 (analytic Fredholm theorem). *Assume that H is a Hilbert space and denote by $L(H)$ the Banach space of all bounded linear operators acting on H . For an open connected set $D \subset \mathbb{C}$, let $f : D \rightarrow L(H)$ be an analytic operator-valued function such that $f(z)$ is compact for each $z \in D$. Then, either*

- (a) $(I - f(z))^{-1}$ exists for no $z \in D$, or
- (b) $(I - f(z))^{-1}$ exists for all $z \in D \setminus S$, where S is a discrete subset of D (*i.e.* a set which has no limit points in D).

A more precise description of $\sigma(\mathcal{L})$ is possible in the case of particular nonlinearities, as stated in Corollary 2.4. First, however, we recall properties of eigenvalues μ and the corresponding eigenfunctions ψ of the following boundary value problem

$$(4.19) \quad \Delta\psi + \mu q\psi = 0 \quad \text{for } x \in \Omega,$$

$$(4.20) \quad \partial_\nu \psi = 0 \quad \text{for } x \in \partial\Omega,$$

with a given potential $q \in L^\infty(\Omega)$. The following two lemmas contain results on the existence of eigenvalues, their continuous dependence on a potential q , and their monotonicity with respect to q .

Lemma 4.12. *Assume that $q \in L^\infty(\Omega)$. Then, there exists a sequence $\{\mu_k(q)\}_{k=0}^\infty$ of eigenvalues of problem (4.19)-(4.20) satisfying $\mu_1(q) < \mu_2(q) < \mu_3(q) \cdots \rightarrow +\infty$.*

Lemma 4.13. *There exists a constant $C > 0$ such that for all $q, \tilde{q} \in L^\infty(\Omega)$ and for all $n \in \mathbb{N} \cup \{0\}$, we have $|\mu_n(q) - \mu_n(\tilde{q})| \leq C\|q - \tilde{q}\|_{L^2(\Omega)}$. Moreover, if $q(x) \leq \tilde{q}(x)$ a.e., then $\mu_n(\tilde{q}) \leq \mu_n(q)$.*

Results stated in these lemmas are classical. Indeed, by a well-known reasoning, it suffices to convert problem (4.19)-(4.20) into an eigenvalue problem for a compact, self-adjoint, nonnegative operator on $L^2(\Omega)$ (as in Part II of the proof of Theorem 2.1). Hence, properties of eigenvalues, stated in these lemmas, result immediately from the abstract theory, see *eg.* [27, Cor. 5.6 and Thm. 5.7].

Proof of Corollary 2.4. As in the proof of Theorem 2.1, we analyze the resolvent equations corresponding to \mathcal{L} stated in (4.11)-(4.13) with $f_u = \lambda_0$.

It follows from equations (4.11)-(4.13) that the operator $\mathcal{L} - \lambda_0 I : D(\mathcal{L}) \rightarrow L^2(\Omega) \times L^2(\Omega)$ is injective. Indeed, setting $\lambda = \lambda_0 = f_u$ and $F = 0$ in equation (4.11) we obtain

that $\psi = 0$ almost everywhere, because $f_v \neq 0$ due to the compensation condition (2.10). Thus, using equation (4.12) with $\psi = 0$ and $G = 0$, we obtain that $\varphi = 0$ because $g_u \neq 0$ by (2.10). Hence, $\text{Ker}(\mathcal{L} - \lambda_0 I) = \{(0, 0)\}$. However, $(\mathcal{L} - \lambda_0 I)^{-1}$ is not well-defined on the whole space $L^2(\Omega) \times L^2(\Omega)$, because, by equation (4.11) with $\lambda = \lambda_0$, the relation $f_v \psi = F$ cannot be true for every $F \in L^2(\Omega)$ and some $\psi \in W^{2,2}(\Omega)$. Thus, the number $\lambda_0 = f_u$ belongs to the continuous spectrum of $(\mathcal{L}, D(\mathcal{L}))$.

Next, if $\lambda \neq f_u$, as it was explained in the proof of Theorem 2.1, it suffices to analyze nontrivial solutions of the boundary value problem in Ω

$$(4.21) \quad \begin{aligned} \Delta \psi + q(\lambda) \psi &= 0 & \text{with } q(\lambda) &= -\frac{g_u f_v}{\lambda_0 - \lambda} + g_v - \lambda \\ \partial_\nu \psi &= 0 & \text{on } \partial\Omega. \end{aligned}$$

Step 1. Notice that the function $q = q(\lambda, \cdot) : \mathbb{R} \setminus \{\lambda_0\} \rightarrow L^2(\Omega)$ is continuous and satisfies $q(\lambda, x) \rightarrow +\infty$ uniformly in $x \in \Omega$ if $\lambda \nearrow \lambda_0$, because of the autocatalysis assumption $g_u f_v < 0$ (here, $q(\lambda, x) \rightarrow +\infty$ also if $g_u f_v > 0$ and if $\lambda \searrow \lambda_0$, see Remark 2.5).

Step 2. By Lemma 4.12, for every $\lambda < \lambda_0$, there exists an increasing sequence

$$\mu_1(q(\cdot, \lambda)) < \mu_2(q(\cdot, \lambda)) < \dots < \mu_n(q(\cdot, \lambda)) < \dots \rightarrow +\infty$$

of eigenvalues of problem (4.19)-(4.20) with $q = q(x, \lambda)$. Our goal is to show that there exists a sequence of real numbers $\lambda_n < \lambda_0$ such that $\mu_n(q(\cdot, \lambda_n)) = 1$. Then, the corresponding eigenfunction of problem (4.19)-(4.20) will be a non-zero solution of (4.21).

Step 3. The eigenvalue $\mu_n(q(\cdot, \lambda))$ is a continuous function of $\lambda < \lambda_0$ for each $n \in \mathbb{N}$. Indeed, this is an immediate consequence of Lemma 4.13, because the mapping $q(\cdot, \lambda) : (-\infty, \lambda_0) \rightarrow L^2(\Omega)$ is continuous.

Step 4. Let us show that $\mu_n(\lambda) \rightarrow 0$ when $\lambda \rightarrow \lambda_0$. By Step 1, we have

$$\omega(\lambda) \equiv \inf_{x \in \Omega} q(x, \lambda) \rightarrow \infty \quad \text{when } \lambda < \lambda_0 \text{ and } \lambda \rightarrow \lambda_0.$$

Since $\omega(\lambda)$ is a positive constant for each $\lambda < \lambda_0$ sufficiently close to λ_0 , then the eigenvalues μ of the problem

$$\begin{aligned} \Delta \psi + \mu \omega(\lambda) \psi &= 0 & \text{in } \Omega \\ \partial_\nu \psi &= 0 & \text{on } \partial\Omega. \end{aligned}$$

has a sequence of eigenvalues $\mu_n(\omega(\lambda)) > 0$ satisfying $\mu_n(\omega(\lambda)) \rightarrow 0$ as $\omega(\lambda) \rightarrow \infty$ for each $n \in \mathbb{N}$. Since $\omega(\lambda) \leq q(x, \lambda)$, the comparison property for eigenvalues stated in Lemma 4.13 implies

$$\mu_n(q(\cdot, \lambda)) \leq \mu_n(\omega(\lambda)) \rightarrow 0 \quad \text{as } \lambda \rightarrow \lambda_0.$$

Conclusion. Since $0 < \mu_1(q(\cdot, \lambda)) < \mu_2(q(\cdot, \lambda)) < \dots < \mu_n(q(\cdot, \lambda)) < \dots \rightarrow +\infty$ and $\lambda_n(q(\cdot, \lambda)) \rightarrow 0$ as $\lambda \rightarrow \lambda_0$, for every $n \in \mathbb{N}$, it follows from the continuous dependence of $\mu_n(q(\cdot, \lambda))$ on λ (see Step 3) that there exists $\lambda_n \rightarrow \lambda_0$ such that $\mu_n(q(\cdot, \lambda_n)) = 1$, provided n is sufficiently large.

Thus, $\sigma(\mathcal{L})$ contains the number $\lambda_0 = f_u > 0$ and a sequence of real numbers $\lambda_n \nearrow \lambda_0$. Notice, however, that the spectrum $\sigma(\mathcal{L})$ may consist also of other complex eigenvalues of the operator \mathcal{L} , according to the reasoning from the proof of Theorem 2.1. \square

Proof of Corollary 2.6. Here, it suffices to follow the proof of Theorem 2.1. First, we linearize our problem at a weak bounded stationary solution (U, V) and we notice that assumptions of Lemmas 4.8–4.9 are satisfied. Next, following the arguments in Part I of the proof of Theorem 2.1, we show that the number $f_u(U(x_0), V(x_0))$ belongs to $\sigma(\mathcal{L})$,

where $f_u(U(x), V(x))$ is positive at x_0 and continuous in its neighborhood. Notice that we do not need to show that all numbers from $\text{Range } f_u(U, V)$ are in $\sigma(\mathcal{L})$ to show the spectral gap condition required by Theorem 4.5. The reasoning from Part II of the proof of Theorem 2.1 can be copied here without any change because $q(\lambda, x)$ defined in (4.16) is a bounded function for every $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$. \square

Proof of Corollary 2.7. Here, the analysis is similar to the case of regular stationary solutions discussed in Theorem 2.1, hence, we only emphasize the most important steps.

Let (U, V) be a weak solution of problem (2.1)-(2.3) and denote by $\mathcal{I} \subset \overline{\Omega}$ its *null* set, namely, a measurable set such that $U(x) = 0$ for all $x \in \mathcal{I}$ and $U(x) \neq 0$ for all $x \in \overline{\Omega} \setminus \mathcal{I}$. For a null set \mathcal{I} , we define the associate L^2 -space

$$L_{\mathcal{I}}^2(\Omega) = \{v \in L^2(\Omega) : v(x) = 0 \text{ for } x \in \mathcal{I}\},$$

supplemented with the usual L^2 -scalar product, which is a Hilbert space as the closed subspace of $L^2(\Omega)$. In the same way, we define the subspace $L_{\mathcal{I}}^\infty(\Omega) \subset L^\infty(\Omega)$ by the equality $L_{\mathcal{I}}^\infty(\Omega) = \{v \in L^\infty(\Omega) : v(x) = 0 \text{ for } x \in \mathcal{I}\}$.

Obviously, when the measure of \mathcal{I} equals zero, we have $L_{\mathcal{I}}^2(\Omega) = L^2(\Omega)$. Assumptions imposed in Corollary 2.7 imply that \mathcal{I} is different from the whole interval.

Now, observe that if $u_0(x) = 0$ for some $x \in \Omega$ then by equations (1.1) with the nonlinearity $f(u, v) = r(u, v)u$ we have $u(x, t) = 0$ for all $t \geq 0$. Hence, the spaces

$$(4.22) \quad X_{\mathcal{I}} = L_{\mathcal{I}}^\infty(\Omega) \times L^\infty(\Omega) \quad \text{and} \quad Z_{\mathcal{I}} = L_{\mathcal{I}}^2(\Omega) \times L^2(\Omega)$$

are invariant for the flow generated by problem (1.1)-(1.4) (notice that there is no “ \mathcal{I} ” in the second coordinates of $X_{\mathcal{I}}$ and $Z_{\mathcal{I}}$). The crucial part of our analysis is based on the fact that, as long as we work in the space $X_{\mathcal{I}}$ and $Z_{\mathcal{I}}$, we can linearize problem (1.1)-(1.4) at the weak solution (U, V) . Moreover, for each $x \in \overline{\Omega} \setminus \mathcal{I}$, the corresponding linearized operator agrees with \mathcal{L} defined in Lemma 4.8. Hence, the analysis from the proof of Theorem 2.1 can be directly adapted to discontinuous steady states in the following way.

We fix a weak stationary solution $(U_{\mathcal{I}}, V_{\mathcal{I}})$ with a null set $\mathcal{I} \subset \Omega$. The Fréchet derivative of the nonlinear mapping $\mathcal{F} : Z_{\mathcal{I}} \rightarrow Z_{\mathcal{I}}$ defined by the mappings $(U, V) \mapsto (f(U, V), g(U, V))$ at the point $(U_{\mathcal{I}}, V_{\mathcal{I}}) \in Z_{\mathcal{I}}$ has the form

$$D\mathcal{F}(U_{\mathcal{I}}, V_{\mathcal{I}}) \begin{pmatrix} \varphi \\ \psi \end{pmatrix} = \mathcal{A}_{\mathcal{I}}(x) \begin{pmatrix} \varphi \\ \psi \end{pmatrix},$$

where

$$\mathcal{A}_{\mathcal{I}}(x) = \begin{pmatrix} f_u(U_{\mathcal{I}}(x), V_{\mathcal{I}}(x)) & f_v(U_{\mathcal{I}}(x), V_{\mathcal{I}}(x)) \\ g_u(U_{\mathcal{I}}(x), V_{\mathcal{I}}(x)) & g_v(U_{\mathcal{I}}(x), V_{\mathcal{I}}(x)) \end{pmatrix}$$

This results immediately from the definition of the Fréchet derivative.

Next, we study spectral properties of the linear operator

$$\mathcal{L}_{\mathcal{I}} \begin{pmatrix} \varphi \\ \psi \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 0 & \Delta \psi \end{pmatrix} + \mathcal{A}_{\mathcal{I}}(x) \begin{pmatrix} \varphi \\ \psi \end{pmatrix},$$

in the Hilbert space $Z_{\mathcal{I}}$ (see (4.22)) with the domain $D(\mathcal{L}_{\mathcal{I}}) = L_{\mathcal{I}}^2(\Omega) \times W^{2,2}(\Omega)$. Here, the reasoning from Part I of the proof of Theorem 2.1 can be directly adapted with a modification as in the proof of Corollary 2.6.

Finally, we study the discrete spectrum of $\mathcal{L}_{\mathcal{I}}$ in the same way as in Part I of the proof of Theorem 2.1 because the corresponding function $q(\lambda, x)$ is bounded for $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$.

The proof of instability of the stationary solution $(U_{\mathcal{I}}, V_{\mathcal{I}})$ is completed by Theorem 4.5 and Lemmas 4.8-4.9. \square

5. CONSTANT AND NON-CONSTANT STATIONARY SOLUTIONS

First, we prove an auxiliary result which will imply Theorem 2.10.

Lemma 5.1. *Assume that $V \in C^2(\Omega) \cap C^1(\overline{\Omega})$ is a non-constant solution to the boundary value problem*

$$(5.1) \quad \Delta V + h(V) = 0 \quad \text{for } x \in \Omega \quad \text{and} \quad \partial_\nu V = 0 \quad \text{for } x \in \partial\Omega.$$

Then, there exists $x_0 \in \overline{\Omega}$ and $a_0 \in \mathbb{R}$ such that

$$(5.2) \quad V(x_0) = a_0, \quad h(a_0) = 0 \quad \text{and} \quad h'(a_0) \geq 0.$$

Proof. First, as in the proof of Proposition 2.9, we integrate the equation in (5.1) and we use the Neumann boundary condition to obtain $\int_\Omega h(V(x)) dx = 0$. Hence, there exists $x_0 \in \overline{\Omega}$ and $a_0 \in \mathbb{R}$ such that $V(x_0) = a_0$ and $h(a_0) = 0$. Now, we suppose that $h'(a_0) < 0$, and consider two cases: $x_0 \in \Omega$ and $x_0 \in \partial\Omega$, separately.

Let $x_0 \in \Omega$. Since $h(a_0) = 0$, we have

$$\Delta(V - a_0) + h(V) - h(a_0) = 0.$$

Using the well-known formula

$$\begin{aligned} h(V) - h(a_0) &= \int_0^1 \frac{d}{ds} h(sV + (1-s)a_0) ds \\ &= (V - a_0) \int_0^1 h'(sV + (1-s)a_0) ds, \end{aligned}$$

we obtain

$$(5.3) \quad \Delta(V - a_0) + r(x, a_0)(V - a_0) = 0,$$

where $r(x, a_0) = \int_0^1 h'(sV(x) + (1-s)a_0) ds$. Observe that $r(\cdot, a_0) \in C(\Omega)$ and

$$\begin{aligned} r(x_0, a_0) &= \int_0^1 h'(sV(x_0) + (1-s)a_0) ds \\ &= \int_0^1 h'(sa_0 + (1-s)a_0) ds \\ &= h'(a_0) < 0. \end{aligned}$$

Hence, there exists an open neighbourhood $\mathcal{U} \subset \Omega$ of x_0 such that $r(x, a_0) < 0$ for all $x \in \mathcal{U}$. Suppose that $r(x, a_0) < 0$ for all $x \in \Omega$. Multiplying both sides of equation (5.3) by $V(x) - a_0$ and integrating over Ω , we obtain

$$-\int_\Omega |\nabla(V(x) - a_0)|^2 dx + \int_\Omega r(x, a_0)(V(x) - a_0)^2 dx = 0.$$

This implies that $V(x) \equiv a_0$, which is a contradiction, because we assume that $V = V(x)$ is a non-constant solution. Therefore, there exists $x_1 \in \partial\mathcal{U} \cap \Omega$ such that $r(x_1, a_0) = 0$. It follows from equation (5.3) that $\Delta V(x_1) = 0$, and consequently, from equation (5.1) we have $h(V(x_1)) = 0$. Hence, there exists $a_1 \in \mathbb{R}$ such that $V(x_1) = a_1$ and $h(a_1) = 0$. Note that $a_1 \neq a_0$. Thus, if the equation $h(V) = 0$ has only one root, the proof of Lemma 5.1 is completed.

Now, we consider two cases.

Case I: The equation $h(V) = 0$ has no solution between a_0 and a_1 . Thus, we define the function

$$\psi(s) = V(x_0 + s(x_1 - x_0)) \quad \text{for } 0 \leq s \leq 1,$$

and, without loss of generality, we can assume that $a_0 < \psi(s) < a_1$ for all $0 < s < 1$.

Since $h(a_0) = 0$ and $h'(a_0) < 0$, we have $h(a_0 + \theta_0) < 0$ for small $\theta_0 > 0$. If we also suppose that $h'(a_1) < 0$, then, we can find small $\theta_1 > 0$ such that $h(a_1 - \theta_1) > 0$. Noting that $\psi(s)$ is continuous function, we see that there exist $s_*, s_{**} \in (0, 1)$ such that $\psi(s_*) = a_0 + \theta_0$ and $\psi(s_{**}) = a_1 - \theta_1$. This implies that there exists $\hat{s} \in (s_*, s_{**})$ for which $h(V(x_0 + \hat{s}(x_1 - x_0))) = 0$, and from the assumption for $\psi(s)$,

$$a_0 < V(x_0 + \hat{s}(x_1 - x_0)) < a_1.$$

This is a contradiction with the hypothesis that the equation $h(V) = 0$ has no roots between a_0 and a_1 . Hence, $h'(a_1) \geq 0$.

Case II: The equation $h(V) = 0$ has a solution a_m between a_0 and a_1 . It is clear that $V(x)$ has to touch a_m , too. Choosing a_m the closest root of $h(V) = 0$ to a_0 , we repeat the argument from Case I to show that $h'(a_m) \geq 0$.

Next, let $x_0 \in \partial\Omega$. Following the previous reasoning and using the hypothesis $h'(a_0) < 0$, we find a ball $B \subseteq \Omega$ such that $x_0 \in \partial\Omega$ and $r(x, a_0) < 0$ for all $x \in B$. Moreover, we can assume that either $V(x) > a_0$ or $V(x) < a_0$ for all $x \in B$, because, if there exists $x_1 \in B$ such that $V(x_1) = a_0$, then we can apply the same argument as in the first part of this proof to obtain $h'(a_0) > 0$.

Let $V(x) < a_0$ for all $x \in B$, and we apply the Hopf boundary lemma to equation (5.3) in the ball B . If V is a non-constant solution satisfying $V(x) - a_0 < 0$ and $V(x_0) - a_0 = 0$, then necessarily $\partial V(x_0)/\partial\nu > 0$, which contradicts the Neumann boundary condition satisfied by V at $x_0 \in \partial\Omega$.

Now, we consider the case $V(x) > a_0$ for all $x \in B$. Here, the function $U(x) = -(V(x) - a_0)$ satisfies the equation

$$-\Delta U + (-r(x, a_0))U = 0 \quad \text{in } B$$

where $r(x, a_0) < 0$, $U(x) < 0$ for all $x \in B$ and $U(x_0) = 0$. Hence, the Hopf boundary lemma yields a contradiction.

Thus, $h'(a_0) \geq 0$ and the proof is complete. \square

Proof of Theorem 2.10. Let $(U(x), V(x))$ be a non-constant regular stationary solution of (1.1)–(1.3) which means that $U = k(V)$ and $f(k(V), V) = 0$. Since each constant solution is non-degenerate, the equation $f(U, V) = 0$ can be solved locally with respect to U , which implies that $k = k(V)$ is a C^1 -function. Substituting $U = k(V)$ into equation (2.2) and denoting $h(V) = g(k(V), V)$, we obtain the following boundary value problem satisfied by $V = V(x)$:

$$(5.4) \quad \Delta V + h(V) = 0 \quad \text{for } x \in \Omega,$$

$$(5.5) \quad \partial_\nu V = 0 \quad \text{for } x \in \partial\Omega.$$

By Lemma 5.1, there exists a constant solution \bar{v} of problem (5.4)–(5.5) and $x_0 \in \bar{\Omega}$ such that

$$(5.6) \quad V(x_0) = \bar{v}, \quad h(\bar{v}) = 0, \quad \text{and} \quad h'(\bar{v}) \geq 0.$$

On the other hand, differentiating the function $h(v) = g(k(v), v)$ yields

$$(5.7) \quad h'(v) = k'(v)g_u(k(v), v) + g_v(k(v), v).$$

Moreover, we differentiate both sides of the equation $f(k(v), v) = 0$ with respect to v to obtain $k'(v)f_u(k(v), v) + f_v(k(v), v) = 0$. Hence,

$$(5.8) \quad k'(v) = -\frac{f_v(k(v), v)}{f_u(k(v), v)}.$$

Finally, choosing $v = \bar{v}$ and $u = \bar{u} = k(\bar{v})$ and substituting equation (5.8) into (5.7), we obtain

$$\begin{aligned} h'(\bar{v}) &= -\frac{f_v(k(\bar{v}), \bar{v})}{f_u(k(\bar{v}), \bar{v})}g_u(k(\bar{v}), \bar{v}) + g_v(k(\bar{v}), \bar{v}) \\ &= \frac{1}{f_u(\bar{u}, \bar{v})} [f_u(\bar{u}, \bar{v})g_v(\bar{u}, \bar{v}) - f_v(\bar{u}, \bar{v})g_u(\bar{u}, \bar{v})] \\ &= \frac{1}{f_u(\bar{u}, \bar{v})} \det \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix}. \end{aligned}$$

By (5.6), it holds $h'(\bar{v}) \geq 0$. Moreover, since (\bar{u}, \bar{v}) is non-degenerate, we obtain $h'(\bar{v}) > 0$. This completes the proof of inequality (2.17). \square

Remark 5.2. Before deriving consequences of inequality (2.17), let us recall properties of a constant solution (\bar{u}, \bar{v}) of the kinetic system of the ordinary differential equations

$$(5.9) \quad \frac{du}{dt} = f(u, v), \quad \frac{dv}{dt} = g(u, v).$$

It is well-known that if

$$(5.10) \quad f_u(\bar{u}, \bar{v}) + g_v(\bar{u}, \bar{v}) < 0 \quad \text{and} \quad \det \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix} > 0,$$

then the Jacobi matrix

$$(5.11) \quad \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix}$$

has all eigenvalues with negative real parts, so, (\bar{u}, \bar{v}) is an asymptotically stable solution of system (5.9). On the other hand, if

$$(5.12) \quad \text{either} \quad f_u(\bar{u}, \bar{v}) + g_v(\bar{u}, \bar{v}) > 0 \quad \text{or} \quad \det \begin{pmatrix} f_u(\bar{u}, \bar{v}) & f_v(\bar{u}, \bar{v}) \\ g_u(\bar{u}, \bar{v}) & g_v(\bar{u}, \bar{v}) \end{pmatrix} < 0,$$

then the linearization matrix (5.11) has an eigenvalue with a positive real part, and consequently, the couple (\bar{u}, \bar{v}) is an unstable solution of (5.9).

Proof of Corollary 2.12. Let (\bar{u}, \bar{v}) be a constant solution of (1.1)-(1.4) for which inequality (2.17) holds true. Using properties of constant solutions to the kinetic system recalled in Remark 5.2 we obtain immediately the following alternative.

If both factors on the left-hand side of inequality (2.17) are positive, then, in particular, the autocatalysis condition $f_u(\bar{u}, \bar{v}) > 0$ is satisfied. Hence, the constant solution (\bar{u}, \bar{v}) is an unstable solution of the reaction-diffusion-ODE system (1.1)-(1.4) by Theorem 2.1.

On the other hand, if both factors on the left-hand side of inequality (2.17) are negative, then the alternative in (5.12) is satisfied and the constant vector (\bar{u}, \bar{v}) is an unstable solution of the corresponding kinetic system (1.1). \square

Proof of Corollary 2.13. Since (\bar{u}, \bar{v}) is an asymptotically stable solution of the kinetic system (5.9), inequality (2.17) together with the second inequality in (5.10) imply immediately the autocatalysis condition $f_u(\bar{u}, \bar{v}) > 0$. Hence, the instability of (\bar{u}, \bar{v}) , as a solution of the reaction-diffusion-ODE problem (1.1)-(1.4), is a direct consequence of Theorem 2.1. \square

Proof of Corollary 2.14. The vector (\bar{u}, \bar{v}) is an asymptotically stable solution of the kinetic system (5.9), hence, inequalities (5.10) hold true (because we assume that (\bar{u}, \bar{v}) is nondegenerate, cf. (2.15)). Thus, calculating the determinant in the second inequality of (5.10) we obtain

$$(5.13) \quad f_v(\bar{u}, \bar{v})g_u(\bar{u}, \bar{v}) < f_u(\bar{u}, \bar{v})g_v(\bar{u}, \bar{v}).$$

Next, by the first inequality in (5.10) and by Corollary 2.13 (see its proof), we have the following two inequalities

$$f_u(\bar{u}, \bar{v}) + g_v(\bar{u}, \bar{v}) < 0 \quad \text{and} \quad f_u(\bar{u}, \bar{v}) > 0,$$

which imply $g_v(\bar{u}, \bar{v}) < 0$ and, consequently, $f_u(\bar{u}, \bar{v})g_v(\bar{u}, \bar{v}) < 0$. Using this estimate in inequality (5.13), we obtain the compensation property (2.10) at the constant steady state (\bar{u}, \bar{v}) . \square

APPENDIX A. MODEL REDUCTION

Initial-boundary value problems for reaction-diffusion-ODE systems arise in the modeling of the growth of a spatially-distributed cell population, where proliferation is controlled by endogenous or exogenous growth factors diffusing in the extracellular medium and binding to cell surface as proposed by Marciniak and Kimmel in the series of recent papers [15, 16, 17]. Here, we consider the following particular case of such systems, which was studied by us in [14]

$$(A.1) \quad \partial_t u_\varepsilon = \left(\frac{av_\varepsilon}{u_\varepsilon + v_\varepsilon} - d_c \right) u_\varepsilon \equiv f(u_\varepsilon, v_\varepsilon),$$

$$(A.2) \quad \varepsilon \partial_t v_\varepsilon = -d_b v_\varepsilon + u_\varepsilon^2 w_\varepsilon - d v_\varepsilon \equiv g(u_\varepsilon, v_\varepsilon, w_\varepsilon),$$

$$(A.3) \quad \partial_t w_\varepsilon - D \Delta w_\varepsilon + d_g w_\varepsilon = -u_\varepsilon^2 w_\varepsilon + d v_\varepsilon + \kappa_0 \equiv h(u_\varepsilon, v_\varepsilon, w_\varepsilon),$$

on $(0, \infty) \times \Omega$, supplemented with zero-flux boundary conditions for w_ε

$$(A.4) \quad \partial_\nu w_\varepsilon(x, t) = 0 \quad \text{for all } t > 0, x \in \partial\Omega$$

and with nonnegative, smooth and bounded initial data

$$(A.5) \quad u_\varepsilon(x, 0) = u_0(x), \quad v_\varepsilon(x, 0) = v_0(x), \quad w_\varepsilon(x, 0) = w_0(x).$$

In equations (A.1)-(A.3), the letters $a, d_c, d_b, d, \kappa_0, D$ denote positive constants.

As it was shown in [14, Sec. 3], solutions of this problem are nonnegative and stay bounded on every interval $[0, T]$. Here, we study the behavior of these solutions as $\varepsilon \rightarrow 0$.

First, we notice that choosing $\varepsilon = 0$ in equation (A.2), we obtain the identity

$$(A.6) \quad v = \frac{u^2 w}{d_b + d}.$$

Substituting it to the two remaining equations (A.1), (A.3) yields the system

$$(A.7) \quad u_t = \left(\frac{auw}{1+uw} - d_c \right) u \quad \text{for } x \in \overline{\Omega}, \ t > 0,$$

$$(A.8) \quad w_t = D\Delta w - d_g w - \frac{d_b}{d_b + d} u^2 w + \kappa_0 \quad \text{for } x \in \Omega, \ t > 0,$$

$$(A.9) \quad \partial_\nu w(x, t) = 0 \quad \text{for } x \in \partial\Omega, \ t > 0,$$

$$(A.10) \quad u(x, 0) = u_0(x) \quad \text{and} \quad w(x, 0) = w_0(x).$$

Repeating our reasoning from [14] one can show that this new system has also a unique, global-in-time nonnegative, smooth solution for nonnegative and smooth initial data.

In this part of Appendix, we show that solutions of the quasi-stationary system (A.6)-(A.10) are good approximation of solutions of the original three-equation model (A.1)-(A.5). Our main result concerns uniform estimates for an approximation error for u and w on each finite time interval $[0, T]$.

First, we show that solutions of ε -problem (A.1)-(A.5) are uniformly bounded with respect to small $\varepsilon > 0$, locally in time.

Lemma A.1. *For every $T > 0$ there exists $C(T) > 0$ such for all sufficiently small $\varepsilon > 0$ (e.g. $\varepsilon \in (0, (d_b + d)/(2d_g))$) the solution of system (A.1)-(A.5) satisfies*

$$\|u_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C(T), \quad \|v_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C(T), \quad \|w_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C(T)$$

for all $t \in [0, T]$.

Proof. Since $v_\varepsilon/(u_\varepsilon + v_\varepsilon) \leq 1$ for nonnegative solutions, equation (A.1) yields the inequality,

$$(A.11) \quad \|u_\varepsilon(t)\|_{L^\infty(\Omega)} \leq M(t) \equiv \|u_0\|_{L^\infty(\Omega)} e^{(a-d_c)t}.$$

Hence, we have the estimate $\|u_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C(T) = \|u_0\|_{L^\infty(\Omega)} e^{(a-d_c)T}$ for all $t \in [0, T]$.

Applying the comparison principle to the parabolic equation (A.3) with the Neumann boundary condition we obtain the estimate

$$(A.12) \quad 0 \leq w_\varepsilon(x, t) \leq \|w_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C_w(t),$$

where the function $C_w = C_w(t)$ satisfies the Cauchy problem

$$(A.13) \quad \begin{aligned} \frac{d}{dt} C_w + d_g C_w &= d \|v_\varepsilon(t)\|_{L^\infty(\Omega)} + \kappa_0 \\ C_w(0) &= \|w_0\|_{L^\infty(\Omega)}, \end{aligned}$$

and is given by the formula

$$(A.14) \quad C_w(t) = \frac{\kappa_0}{d_g} + \left(\|w_0\|_{L^\infty(\Omega)} - \frac{\kappa_0}{d_g} \right) e^{-d_g t} + d \int_0^t e^{-d_g(t-\tau)} \|v_\varepsilon(\tau)\|_{L^\infty(\Omega)} d\tau.$$

Next, we use equation (A.2) to obtain

$$(A.15) \quad \|v_\varepsilon(t)\|_{L^\infty(\Omega)} \leq \|v_0\|_{L^\infty(\Omega)} e^{-\frac{d_b+d}{\varepsilon}t} + \frac{1}{\varepsilon} \int_0^t M^2(\tau) \|w_\varepsilon(\tau)\|_{L^\infty(\Omega)} e^{-\frac{d_b+d}{\varepsilon}(t-\tau)} d\tau.$$

Thus, using inequality (A.11) and plugging the above estimate into (A.14) yields

$$(A.16) \quad \begin{aligned} C_w(t) &\leq \frac{\kappa_0}{d_g} + \left(\|w_0\|_{L^\infty(\Omega)} - \frac{\kappa_0}{d_g} \right) e^{-d_g t} + d \|v_0\|_{L^\infty(\Omega)} \int_0^t e^{-d_g(t-\tau)} e^{-\frac{d_b+d}{\varepsilon}\tau} d\tau \\ &\quad + \frac{d \|u_0\|_{L^\infty(\Omega)}}{\varepsilon} \int_0^t e^{-d_g(t-\tau)} \int_0^\tau e^{(a-d_c)\xi} \|w_\varepsilon(\xi)\|_{L^\infty(\Omega)} e^{-\frac{d_b+d}{\varepsilon}(\tau-\xi)} d\xi d\tau. \end{aligned}$$

Changing the order of integration, we can simplify the last term on the right-hand side

$$\begin{aligned} & \int_0^t e^{-d_g(t-\tau)} \int_0^\tau e^{(a-d_c)\xi} \|w_\varepsilon(\xi)\|_{L^\infty(\Omega)} e^{-\frac{d_b+d}{\varepsilon}(\tau-\xi)} d\xi d\tau \\ &= \int_0^t \frac{\varepsilon \|w_\varepsilon(\xi)\|_{L^\infty(\Omega)}}{d_b+d-\varepsilon d_g} e^{-d_g(t-\xi)} e^{(a-d_c)\xi} d\xi - \int_0^t \frac{\varepsilon \|w_\varepsilon(\xi)\|_{L^\infty(\Omega)}}{d_b+d-\varepsilon d_g} e^{(a-d_c)\xi} e^{\frac{d_b+d}{\varepsilon}(\xi-t)} d\xi \end{aligned}$$

hence, for $0 < \varepsilon < \frac{d_b+d}{d_g}$, using inequalities (A.12) we obtain

$$(A.17) \quad \|w_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C + \frac{d\|u_0\|_{L^\infty(\Omega)}}{d_b+d-\varepsilon d_g} \int_0^t e^{(a-d_c)\xi} \|w_\varepsilon(\xi)\|_{L^\infty(\Omega)} e^{-d_g(t-\xi)} d\xi,$$

where $C = C(\|w_0\|_{L^\infty(\Omega)}, \|v_0\|_{L^\infty(\Omega)})$ is independent of T and of ε . Finally, the Gronwall inequality applied to (A.17) implies the estimate

$$(A.18) \quad \|w_\varepsilon(t)\|_{L^\infty(\Omega)} \leq C e^{C_1(T)} \quad \text{for all } 0 \leq t \leq T$$

and for all sufficiently small $\varepsilon > 0$ (e.g. $\varepsilon \in (0, (d_b+d)/(2d_g))$), where positive constants C and $C_1(T)$ are independent of ε .

Finally, estimate (A.18) applied to inequality (A.15) implies an analogous bound for v_ε . \square

Theorem A.2. *Let $(u_\varepsilon, v_\varepsilon, w_\varepsilon)$ be a solution of system (A.1)–(A.5) with sufficiently small $\varepsilon > 0$ (e.g. $\varepsilon \in (0, (d_b+d)/(2d_g))$) and (u, w) be a solution of the corresponding system (A.6)–(A.10). For each $T > 0$, there exists a constant $C(T) > 0$ independent of ε such that*

$$(A.19) \quad \max_{t \in [0, T]} \|u_\varepsilon(t) - u(t)\|_{L^\infty(\Omega)} \leq C(T)\varepsilon,$$

$$(A.20) \quad \max_{t \in [0, T]} \|w_\varepsilon(t) - w(t)\|_{L^\infty(\Omega)} \leq C(T)\varepsilon.$$

Additionally, we also have

$$(A.21) \quad \int_0^T \|v_\varepsilon(t) - v(t)\|_{L^\infty(\Omega)} \leq C(T)\varepsilon,$$

where v is given by equation (A.6).

Proof. Letting $\alpha = u_\varepsilon - u$, $\beta = v_\varepsilon - v$ and $\delta = w_\varepsilon - w$, we obtain by the Taylor expansion the following system

$$(A.22) \quad \partial_t \alpha = f(u_\varepsilon, v_\varepsilon) - f(u, v) = -d_c \alpha + f_1 \alpha + f_2 \beta,$$

$$(A.23) \quad \partial_t \varepsilon \beta = g(u_\varepsilon, v_\varepsilon, w_\varepsilon) - g(u, v, w) - \varepsilon \partial_t v = -(d + d_b) \beta + g_1 \alpha + g_2 \delta - \varepsilon \partial_t v,$$

$$(A.24) \quad \partial_t \delta - D \Delta \delta_{xx} + (d_g + g_2) \delta = h_1 \alpha + d \beta,$$

supplemented with the initial conditions

$$\alpha(x, 0) = 0, \quad \delta(x, 0) = 0, \quad \beta(x, 0) = v_0(x) - \tilde{v}_0(x)$$

with \tilde{v}_0 obtained from u_0 and w_0 via formula (A.6), and with the Neumann boundary condition for $\delta(x, t)$. In equations (A.22)–(A.24) the following coefficients

$$\begin{aligned} f_1 &= \frac{\partial f}{\partial u} + d_c = \frac{(av)^2}{(u+v)^2}, & f_2 &= \frac{\partial f}{\partial v} = \frac{(au)^2}{(u+v)^2}, \\ g_1 &= \frac{\partial g}{\partial u} = 2uw, & g_2 &= \frac{\partial g}{\partial w} = -\frac{\partial h}{\partial w} = u^2, & h_1 &= \frac{\partial h}{\partial u} = -2uw \end{aligned}$$

are calculated in certain intermediate points and are bounded independently of ε due to Lemma A.1.

The proof is divided into three steps.

Step 1: First, applying the comparison principle to the parabolic equation (A.3) with the Neumann boundary condition and with the zero initial datum we obtain the estimate

$$\|\delta(\cdot, t)\|_{L^\infty(\Omega)} \leq C_\delta(t) \quad \text{for every } t \in [0, T],$$

where C_δ is a solution of the Cauchy problem

$$\begin{aligned} C_\delta(0) &= 0, \\ \frac{d}{dt} C_\delta + (d_g + \|g_2\|_{L^\infty(\Omega \times [0, T])}) C_\delta &= \|h_1\|_{L^\infty(\Omega \times [0, T])} \|\alpha(t)\|_{L^\infty(\Omega)} + d \|\beta(t)\|_{L^\infty(\Omega)}. \end{aligned}$$

Since

$$C_\delta(t) = \int_0^t e^{-(d_g + \|g_2\|_{L^\infty(\Omega \times [0, T])})(t-\tau)} (\|h_1\|_{L^\infty(\Omega \times [0, T])} \|\alpha(t)\|_{L^\infty(\Omega)} + d \|\beta(t)\|_{L^\infty(\Omega)}) d\tau$$

using the Young inequality for a convolution and the estimate $e^{-(d_g + \|g_2\|_{L^\infty(\Omega \times [0, T])})(t-\tau)} \leq 1$, we obtain

$$(A.25) \quad \|\delta(\cdot, t)\|_{L^\infty(\Omega)} \leq \|C_\delta\|_{L^\infty(0, t)} \leq \|h_1\|_{L^\infty(\Omega \times [0, T])} \|\alpha\|_{L^1(0, t; L^\infty(\Omega))} + d \|\beta\|_{L^1(0, t; L^\infty(\Omega))}.$$

Step 2: Next, we estimate the solution $\beta = \beta(x, t)$ of equation (A.23). First, note that

$$\|e^{-(d+d_b)\frac{\tau}{\varepsilon}}\|_{L^1(0, t)} \leq \frac{\varepsilon}{d+d_b} \quad \text{for all } t > 0.$$

The solution of equation (A.23) satisfies the formula

$$\beta(x, t) = \beta(x, 0) e^{-\frac{d+d_b}{\varepsilon}t} + \int_0^t e^{-\frac{d+d_b}{\varepsilon}(t-\tau)} \left(-\partial_\tau v + \frac{1}{\varepsilon}(g_1\alpha + g_2\delta) \right) d\tau.$$

Consequently, the Young inequality yields

$$\begin{aligned} & \|\beta\|_{L^1(0, t; L^\infty(\Omega))} \\ & \leq (\|\beta(0)\|_{L^\infty(\Omega)} + \|\partial_\tau v\|_{L^1(0, t; L^\infty(\Omega))}) C\varepsilon \\ (A.26) \quad & + C\|g_1\|_{L^\infty(\Omega \times [0, T])} \|\alpha\|_{L^1(0, t; L^\infty(\Omega))} + C\|g_2\|_{L^\infty(\Omega \times [0, T])} \|\delta\|_{L^1(0, t; L^\infty(\Omega))} \\ & \leq C\varepsilon + C(\|g_1\|_{L^\infty(\Omega \times [0, T])} + t\|h_1\|_{L^\infty(\Omega \times [0, T])} \|g_2\|_{L^\infty(\Omega \times [0, T])}) \|\alpha\|_{L^1(0, t; L^\infty(\Omega))} \\ & + Ctd\|g_2\|_{L^\infty(\Omega \times [0, T])} \|\beta\|_{L^1(0, t; L^\infty(\Omega))}, \end{aligned}$$

where the last inequality results from (A.25).

Step 3: Finally, we estimate the solution $\alpha = \alpha(x, t)$ of equation (A.22). Note that $\alpha(x, 0) = 0$ and

$$\alpha(t, x) = - \int_0^t \left(f_2(\tau) \beta(\tau) e^{-d_c(t-\tau) + \int_\tau^t f_1(\xi) d\xi} \right) d\tau.$$

Thus, using the Young inequality again we obtain the estimate

$$(A.27) \quad \|\alpha\|_{L^\infty((0, t) \times \Omega)} \leq C e^{(a-d_c)T} \|f_2\|_{L^\infty(\Omega)} \|\beta\|_{L^1(0, t; L^\infty(\Omega))}$$

as well as

$$(A.28) \quad \|\alpha\|_{L^1(0, t; L^\infty(\Omega))} \leq Ct \|\beta\|_{L^1(0, t; L^\infty(\Omega))}.$$

Inserting inequality (A.28) into (A.26) leads to

$$(A.29) \quad \|\beta\|_{L^1(0, t; L^\infty(\Omega))} \leq C\varepsilon + Ct \|\beta\|_{L^1(0, t; L^\infty(\Omega))}.$$

For $t \leq t_0 = \frac{1}{2C}$ we conclude that

$$(A.30) \quad \|\beta\|_{L^1(0,t;L^\infty(\Omega))} \leq C\varepsilon \quad \text{for all } t \leq t_0.$$

Since every $t \in (t_0, T]$ can be reached after a finite number of steps, estimate (A.30) holds for every $t \in [0, T]$. Furthermore, inequality (A.30) applied in (A.25) and (A.27) completes the proof of estimates (A.19)–(A.21). \square

Remark A.3. To obtain a better estimate of β , one should construct an initial value layer, since $\beta|_{t=0} \neq 0$.

APPENDIX B. CONSTANT STEADY STATES

Here, we consider the space homogeneous solutions of the two-equation model (A.6)–(A.10) which satisfy the corresponding kinetic system

$$(B.1) \quad u_t = \left(\frac{auw}{d_b + d + uw} - d_c \right) u,$$

$$(B.2) \quad w_t = -d_g w - \frac{d_b}{d_b + d} u^2 w + \kappa_0,$$

where $a, d_c, d_b, d, d_g, \kappa_0$ are positive constants and we have always assumed that $a > d_c$. The structure of constant steady states of this system is the same as of the original three-equation model and can be characterized by the following lemma (for the proof see [14]).

Lemma B.1. *Let $\Theta = 4d_g \left(\frac{d_c}{a - d_c} \right)^2 d_b(d_b + d)$. If $\kappa_0^2 > \Theta$, then system (B.1)–(B.2) has two positive steady states (u_-, w_-) and (u_+, w_+) with*

$$(B.3) \quad u_\pm = \frac{d_c}{a - d_c} (d_b + d) \frac{1}{w_\pm} \quad \text{and} \quad w_\pm = \frac{\kappa_0 \pm \sqrt{\kappa_0^2 - \Theta}}{2d_g}.$$

Theorem B.2. *Let (u_-, w_-) and (u_+, w_+) be positive steady states of system (B.1)–(B.2) given by (B.3). Then (u_+, w_+) is always unstable. While (u_-, w_-) is stable, except for the case*

$$\frac{d_c}{a}(a - d_c) - d_g > 0, \quad \frac{\beta}{2} \leq 1 \quad \text{and} \quad \kappa_0^2 \leq \frac{\beta^2 \Theta}{4(\beta - 1)},$$

where

$$\beta = \frac{\frac{d_c}{a}(a - d_c)}{\frac{d_c}{a}(a - d_c) - d_g} > 1.$$

Proof. Let (\bar{u}, \bar{w}) denote a steady state of (B.1)–(B.2). From direct calculations, the Jacobian matrix J at (\bar{u}, \bar{w}) of the nonlinear mapping defined by the right-hand side of (B.1)–(B.2) is of the form

$$J = \begin{pmatrix} \frac{d_c}{a}(a - d_c) & \frac{(a - d_c)^2}{a(d_b + d)} \bar{u}^2 \\ -2\frac{d_b d_c}{a - d_c} & -d_g - \frac{d_b}{d_b + d} \bar{u}^2 \end{pmatrix}.$$

We know (cf. Remark 5.2) that

(i) if

$$(B.4) \quad \frac{d_c}{a}(a - d_c) - d_g - \frac{d_b}{d_b + d}\bar{u}^2 < 0 \quad \text{and} \quad -\frac{d_g d_c}{a}(a - d_c) + \frac{d_b d_c(a - d_c)}{a(d_b + d)}\bar{u}^2 > 0,$$

then all eigenvalues of J have negative real parts;

(ii) if

$$(B.5) \quad \frac{d_c}{a}(a - d_c) - d_g - \frac{d_b}{d_b + d}\bar{u}^2 > 0 \quad \text{or} \quad -\frac{d_g d_c}{a}(a - d_c) + \frac{d_b d_c(a - d_c)}{a(d_b + d)}\bar{u}^2 < 0,$$

then there is an eigenvalue of J which has a positive real part.

Step 1. First, we show the stability of (u_+, w_+) . Using estimates (B.3), the second inequality of (B.5) can be written in the form

$$(B.6) \quad \frac{d_b(d_b + d)}{d_g} \left(\frac{a - d_c}{d_c} \right)^2 < \bar{w}^2.$$

Note that the left-hand side of (B.6) satisfies

$$\frac{d_b(d_b + d)}{d_g} \left(\frac{a - d_c}{d_c} \right)^2 = \frac{\Theta}{4d_g^2}.$$

and w_+ satisfies $(\kappa_0/(2d_g))^2 < w_+^2 < (\kappa_0/d_g)^2$. Therefore, it follows from the assumption $\kappa_0^2 > \Theta$ that

$$\frac{\Theta}{4d_g^2} < \frac{\kappa_0^2}{4d_g^2} < w_+^2,$$

which implies that the steady state (u_+, w_+) is unstable.

Step 2. Next, we show stability of (u_-, w_-) . The second inequality of (B.4) is equivalent to $\Theta/(4d_g^2) > \bar{w}^2$. The latter inequality holds true, since $w_-^2 = \frac{2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta}{4d_g^2}$ and

$$\Theta - \left(2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta \right) = 2\sqrt{\kappa_0^2 - \Theta} \left(\kappa_0 - \sqrt{\kappa_0^2 - \Theta} \right) > 0.$$

Using (B.3) and the relationship $d_b(d_b + d) \left(\frac{d_c}{a - d_c} \right)^2 = \frac{\Theta}{4d_g^2}$, the first condition of (B.4) becomes

$$w_-^2 \left[\frac{d_c}{a}(a - d_c) - d_g \right] < \frac{\Theta}{4d_g}.$$

If $\frac{d_c}{a}(a - d_c) - d_g \leq 0$, then the above inequality always holds.

Assume $\frac{d_c}{a}(a - d_c) - d_g > 0$. Note that w_-^2 is given by

$$w_-^2 = \frac{2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta}{4d_g^2}.$$

Therefore, it is sufficient to show the following inequality

$$(B.7) \quad \left[2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta \right] \left[\frac{d_c}{a}(a - d_c) - d_g \right] < d_g \Theta.$$

The left-hand side of (B.7) is

$$\begin{aligned} & \left[2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta \right] \left[\frac{d_c}{a}(a - d_c) - d_g \right] \\ &= \frac{d_c}{a}(a - d_c) \left[2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta \right] - d_g \left[2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} \right] + d_g\Theta. \end{aligned}$$

Hence, if

$$(B.8) \quad \frac{d_c}{a}(a - d_c) \left[2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} - \Theta \right] - d_g \left[2\kappa_0^2 - 2\kappa_0\sqrt{\kappa_0^2 - \Theta} \right] < 0,$$

then inequality (B.7) holds true. Noting $\frac{d_c}{a}(a - d_c) - d_g > 0$, we obtain, from (B.8), that

$$(B.9) \quad 2 \left[\kappa_0^2 - \kappa_0\sqrt{\kappa_0^2 - \Theta} \right] < \frac{\frac{d_c}{a}(a - d_c)}{\frac{d_c}{a}(a - d_c) - d_g} \Theta = \beta\Theta,$$

what is equivalent to

$$(B.10) \quad \kappa_0^2 - \frac{\beta}{2}\Theta < \kappa_0\sqrt{\kappa_0^2 - \Theta}.$$

If $\beta/2 > 1$ and $\Theta < \kappa_0^2 \leq (\beta/2)\Theta$, then inequality (B.10) is always satisfied since the right-hand side of (B.10) is positive. The remaining cases are (i) $\beta/2 \leq 1$ and (ii) $\beta/2 > 1$ and $\kappa_0^2 > (\beta/2)\Theta$. In the cases (i) and (ii), the both-sides of (B.10) are positive. Therefore, we calculate the square of both sides of (B.10) and obtain

$$(B.11) \quad \frac{\beta^2}{4(\beta - 1)}\Theta < \kappa_0^2.$$

If $\beta > 2$, then $\beta/2 > \beta^2/(4(\beta - 1))$, while $\beta/2 \leq \beta^2/(4(\beta - 1))$ if $\beta \leq 2$. Therefore, the inequality (B.10) holds in case (ii). In case (i), (B.10) is satisfied under the condition (B.11). \square

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